PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶:
C12N 15/31, C07K 14/315, 16/12, C12N 5/18, 1/21, A61K 39/09, C12Q 1/68, G01N 33/50

(11) International Publication Number:

WO 98/18930

(43) International Publication Date:

7 May 1998 (07.05.98)

(21) International Application Number:

PCT/US97/19422

A2

(22) International Filing Date:

30 October 1997 (30.10.97)

(30) Priority Data:

60/029,960

31 October 1996 (31.10.96)

us

(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): KUNSCH, Charles, A. [US/US]; 2398B Dunwoody Crossing, Atlanta, GA 30338 (US). CHOI, Gil, H. [KR/US]; 11429 Potomac Oaks Drive, Rockville, MD 20850 (US). JOHNSON, L., Sydnor [US/US]; 13545 Ambassador Drive, Germantown, MD 20874 (US). HROMOCKYJ, Alex [US/US]; 10003 Sidney Road, Silver Spring, MD 20901 (US).
- (74) Agents: BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: STREPTOCOCCUS PNEUMONIAE ANTIGENS AND VACCINES

(57) Abstract

The present invention relates to novel vaccines for the prevention or attenuation of infection by *Streptococcus pneumoniae*. The invention further relates to isolated nucleic acid molecules encoding antigenic polypeptides of *Streptococcus pneumoniae*. Antigenic polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. The invention additionally relates to diagnostic methods for detecting *Streptococcus* nucleic acids, polypeptides and antibodies in a biological sample.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

of America

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan -
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	1E	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of Ameri
CA	Canada	lТ	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Кепуа	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM ·	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	·Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Streptococcus pneumoniae Antigens and Vaccines

Field of the Invention

5

10

15

20

25

30

35

The present invention relates to novel *Streptococcus pneumoniae* antigens for the detection of *Streptococcus* and for the prevention or attenuation of disease caused by *Streptococcus*. The invention further relates to isolated nucleic acid molecules encoding antigenic polypeptides of *S. pneumoniae*. Antigenic polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. The invention additionally relates to diagnostic methods for detecting *Streptococcus* gene expression.

Background of the Invention

Streptococcus pneumoniae has been one of the most extensively studied microorganisms since its first isolation in 1881. It was the object of many investigations that led to important scientific discoveries. In 1928, Griffith observed that when heat-killed encapsulated pneumococci and live strains constitutively lacking any capsule were concomitantly injected into mice, the nonencapsulated could be converted into encapsulated pneumococci with the same capsular type as the heat-killed strain. Years later, the nature of this "transforming principle," or carrier of genetic information, was shown to be DNA. (Avery, O.T., et al., J. Exp. Med., 79:137-157 (1944)).

In spite of the vast number of publications on *S. pneumoniae* many questions about its virulence are still unanswered, and this pathogen remains a major causative agent of serious human disease, especially community-acquired pneumonia. (Johnston, R.B., et al., Rev. Infect. Dis. 13(Suppl. 6):S509-517 (1991)). In addition, in developing countries, the pneumococcus is responsible for the death of a large number of children under the age of 5 years from pneumococcal pneumonia. The incidence of pneumococcal disease is highest in infants under 2 years of age and in people over 60 years of age. Pneumococci are the second most frequent cause (after *Haemophilus influenzae* type b) of bacterial meningitis and otitis media in children. With the recent introduction of conjugate vaccines for *H. influenzae* type b, pneumococcal meningitis is likely to become increasingly prominent. *S. pneumoniae* is the most important etiologic agent of community-acquired pneumonia in adults and is the second most common cause of bacterial meningitis behind *Neisseria meningitidis*.

The antibiotic generally prescribed to treat *S. pneumoniae* is benzylpenicillin, although resistance to this and to other antibiotics is found occasionally. Pneumococcal resistance to penicillin results from mutations in its

2

penicillin-binding proteins. In uncomplicated pneumococcal pneumonia caused by a sensitive strain, treatment with penicillin is usually successful unless started too late. Erythromycin or clindamycin can be used to treat pneumonia in patients hypersensitive to penicillin, but resistant strains to these drugs exist. Broad spectrum antibiotics (e.g., the tetracyclines) may also be effective, although tetracycline-resistant strains are not rare. In spite of the availability of antibiotics, the mortality of pneumococcal bacteremia in the last four decades has remained stable between 25 and 29%. (Gillespie, S.H., et al., J. Med. Microbiol. 28:237-248 (1989).

5

10

15

20

25

30

35

S. pneumoniae is carried in the upper respiratory tract by many healthy individuals. It has been suggested that attachment of pneumococci is mediated by a disaccharide receptor on fibronectin, present on human pharyngeal epithelial cells. (Anderson, B.J., et al., J. Immunol. 142:2464-2468 (1989). The mechanisms by which pneumococci translocate from the nasopharynx to the lung, thereby causing pneumonia, or migrate to the blood, giving rise to bacteremia or septicemia, are poorly understood. (Johnston, R.B., et al., Rev. Infect. Dis. 13(Suppl. 6):S509-517 (1991).

Various proteins have been suggested to be involved in the pathogenicity of S. pneumoniae, however, only a few of them have actually been confirmed as virulence factors. Pneumococci produce an IgA1 protease that might interfere with host defense at mucosal surfaces. (Kornfield, S.J., et al., Rev. Inf. Dis. 3:521-534 (1981). S. pneumoniae also produces neuraminidase, an enzyme that may facilitate attachment to epithelial cells by cleaving sialic acid from the host glycolipids and gangliosides. Partially purified neuraminidase was observed to induce meningitis-like symptoms in mice; however, the reliability of this finding has been questioned because the neuraminidase preparations used were probably contaminated with cell wall products. Other pneumococcal proteins besides neuraminidase are involved in the adhesion of pneumococci to epithelial and endothelial cells. These pneumococcal proteins have as yet not been identified. Recently, Cundell et al., reported that peptide permeases can modulate pneumococcal adherence to epithelial and endothelial cells. It was, however, unclear whether these permeases function directly as adhesions or whether they enhance adherence by modulating the expression of pneumococcal adhesions. (DeVelasco, E.A., et al., Micro. Rev. 59:591-603 A better understanding of the virulence factors determining its pathogenicity will need to be developed to cope with the devastating effects of pneumococcal disease in humans.

Ironically, despite the prominent role of *S. pneumoniae* in the discovery of DNA, little is known about the molecular genetics of the organism. The *S. pneumoniae* genome consists of one circular, covalently closed, double-stranded DNA and a collection of so-called variable accessory elements, such as prophages, plasmids, transposons and the like. Most physical characteristics and almost all of the genes of *S. pneumoniae* are unknown. Among the few that have been identified, most have not been physically mapped or characterized in detail. Only a few genes of this organism have been sequenced. (See, for instance current versions of GENBANK and other nucleic acid databases, and references that relate to the genome of *S. pneumoniae* such as those set out elsewhere herein.) Identification of *in vivo*-expressed, and broadly protective, antigens of *S. pneumoniae* has remained elusive.

Summary of the Invention

5

10

15

20

25

30

35

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding the *S. pneumoniae* polypeptides described in Table 1 and having the amino acid sequences shown as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and so on through SEQ ID NO:226. Thus, one aspect of the invention provides isolated nucleic acid molecules comprising polynucleotides having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence encoding any of the amino acid sequences of the polypeptides shown in Table 1; and (b) a nucleotide sequence complementary to any of the nucleotide sequences in (a).

Further embodiments of the invention include isolated nucleic acid molecules that comprise a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical, to any of the nucleotide sequences in (a) or (b) above, or a polynucleotide which hybridizes under stringent hybridization conditions to a polynucleotide in (a) or (b) above. This polynucleotide which hybridizes does not hybridize under stringent hybridization conditions to a polynucleotide having a nucleotide sequence consisting of only A residues or of only T residues. Additional nucleic acid embodiments of the invention relate to isolated nucleic acid molecules comprising polynucleotides which encode the amino acid sequences of epitope-bearing portions of an *S. pneumoniae* polypeptide having an amino acid sequence in (a) above.

The present invention also relates to recombinant vectors, which include the isolated nucleic acid molecules of the present invention, and to host cells containing the recombinant vectors, as well as to methods of making such

PCT/US97/19422

5

10

15

20

25

30

35

vectors and host cells and for using these vectors for the production of S. pneumoniae polypeptides or peptides by recombinant techniques.

The invention further provides isolated *S. pneumoniae* polypeptides having an amino acid sequence selected from the group consisting of an amino acid sequence of any of the polypeptides described in Table 1.

The polypeptides of the present invention also include polypeptides having an amino acid sequence with at least 70% similarity, and more preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similarity to those described in Table 1, as well as polypeptides having an amino acid sequence at least 70% identical, more preferably at least 75% identical, and still more preferably 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to those above; as well as isolated nucleic acid molecules encoding such polypeptides.

The present invention further provides a vaccine, preferably a multi-component vaccine comprising one or more of the *S. pneumoniae* polynucleotides or polypeptides described in Table 1, or fragments thereof, together with a pharmaceutically acceptable diluent, carrier, or excipient, wherein the *S. pneumoniae* polypeptide(s) are present in an amount effective to elicit an immune response to members of the *Streptococcus* genus in an animal. The *S. pneumoniae* polypeptides of the present invention may further be combined with one or more immunogens of one or more other streptococcal or non-streptococcal organisms to produce a multi-component vaccine intended to elicit an immunological response against members of the *Streptococcus* genus and, optionally, one or more non-streptococcal organisms.

The vaccines of the present invention can be administered in a DNA form, e.g., "naked" DNA, wherein the DNA encodes one or more streptococcal polypeptides and, optionally, one or more polypeptides of a non-streptococcal organism. The DNA encoding one or more polypeptides may be constructed such that these polypeptides are expressed fusion proteins.

The vaccines of the present invention may also be administered as a component of a genetically engineered organism. Thus, a genetically engineered organism which expresses one or more *S. pneumoniae* polypeptides may be administered to an animal. For example, such a genetically engineered organism may contain one or more *S. pneumoniae* polypeptides of the present invention intracellularly, on its cell surface, or in its periplasmic space. Further, such a genetically engineered organism may secrete one or more *S. pneumoniae* polypeptides.

5

The vaccines of the present invention may be co-administered to an animal with an immune system modulator (e.g., CD86 and GM-CSF).

The invention also provides a method of inducing an immunological response in an animal to one or more members of the *Streptococcus* genus, preferrably one or more isolates of the *S. pneumoniae* genus, comprising administering to the animal a vaccine as described above.

5

10

15

20

25

30

35

The invention further provides a method of inducing a protective immune response in an animal, sufficient to prevent or attenuate an infection by members of the *Streptococcus* genus, preferrably at least *S. pneumoniae*, comprising administering to the animal a composition comprising one or more of the polynucleotides or polypeptides described in Table 1, or fragments thereof. Further, these polypeptides, or fragments thereof, may be conjugated to another immunogen and/or administered in admixture with an adjuvant.

The invention further relates to antibodies elicited in an animal by the administration of one or more *S. pneumoniae* polypeptides of the present invention and to methods for producing such antibodies.

The invention also provides diagnostic methods for detecting the expression of genes of members of the *Streptococcus* genus in an animal. One such method involves assaying for the expression of a gene encoding S. pneumoniae peptides in a sample from an animal. This expression may be assayed either directly (e.g., by assaying polypeptide levels using antibodies elicited in response to amino acid sequences described in Table 1) or indirectly (e.g., by assaying for antibodies having specificity for amino acid sequences described in Table 1). An example of such a method involves the use of the polymerase chain reaction (PCR) to amplify and detect *Streptococcus* nucleic acid sequences.

The present invention also relates to nucleic acid probes having all or part of a nucleotide sequence described in Table 1 (shown as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, and so on through SEQ ID NO:225) which are capable of hybridizing under stringent conditions to *Streptococcus* nucleic acids. The invention further relates to a method of detecting one or more *Streptococcus* nucleic acids in a biological sample obtained from an animal, said one or more nucleic acids encoding *Streptococcus* polypeptides, comprising: (a) contacting the sample with one or more of the above-described nucleic acid probes, under conditions such that hybridization occurs, and (b) detecting hybridization of said one or more probes to the *Streptococcus* nucleic acid present in the biological sample.

5

10

15

20

25

30

35

The invention also includes immunoassays, including an immunoassay for detecting *Streptococcus*, preferrably at least isolates of the *S. pneumoniae* genus, comprising incubation of a sample (which is suspected of being infected with *Streptococcus*) with a probe antibody directed against an antigen/epitope of *S. pneumoniae*, to be detected under conditions allowing the formation of an antigen-antibody complex; and detecting the antigen-antibody complex which contains the probe antibody. An immunoassay for the detection of antibodies which are directed against a *Streptococcus* antigen comprising the incubation of a sample (containing antibodies from a mammal suspected of being infected with *Streptococcus*) with a probe polypeptide including an epitope of *S. pneumoniae*, under conditions that allow the formation of antigen-antibody complexes which contain the probe epitope containing antigen.

Some aspects of the invention pertaining to kits are those for: investigating samples for the presence of polynucleotides derived from *Streptococcus* which comprise a polynucleotide probe including a nucleotide sequence selected from Table 1 or a fragment thereof of approximately 15 or more nucleotides, in an appropriate container; analyzing the samples for the presence of antibodies directed against a *Streptococcus* antigen made up of a polypeptide which contains a *S. pneumoniae* epitope present in the polypeptide, in a suitable container; and analyzing samples for the presence of *Streptococcus* antigens made up of an anti-*S. pneumoniae* antibody, in a suitable container.

Detailed Description

The present invention relates to recombinant antigenic *S. pneumoniae* polypeptides and fragments thereof. The invention also relates to methods for using these polypeptides to produce immunological responses and to confer immunological protection to disease caused by members of the genus *Streptococcus*, at least isolates of the *S. pneumoniae* genus. The invention further relates to nucleic acid sequences which encode antigenic *S. pneumoniae* polypeptides and to methods for detecting *S. pneumoniae* nucleic acids and polypeptides in biological samples. The invention also relates to *S. pneumoniae*-specific antibodies and methods for detecting such antibodies produced in a host animal.

Definitions

The following definitions are provided to clarify the subject matter which the inventors consider to be the present invention.

5

10

15

20

25

30

35

As used herein, the phrase "pathogenic agent" means an agent which causes a disease state or affliction in an animal. Included within this definition, for examples, are bacteria, protozoans, fungi, viruses and metazoan parasites which either produce a disease state or render an animal infected with such an organism susceptible to a disease state (e.g., a secondary infection). Further included are species and strains of the genus *Streptococcus* which produce disease states in animals.

As used herein, the term "organism" means any living biological system, including viruses, regardless of whether it is a pathogenic agent.

As used herein, the term "Streptococcus" means any species or strain of bacteria which is members of the genus Streptococcus. Such species and strains are known to those of skill in the art, and include those that are pathogenic and those that are not.

As used herein, the phrase "one or more *S. pneumoniae* polypeptides of the present invention" means polypeptides comprising the amino acid sequence of one or more of the *S. pneumoniae* polypeptides described in Table 1 and disclosed as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and so on through SEQ ID NO:226. These polypeptides may be expressed as fusion proteins wherein the *S. pneumoniae* polypeptides of the present invention are linked to additional amino acid sequences which may be of streptococcal or non-streptococcal origin. This phrase further includes polypeptide comprising fragments of the *S. pneumoniae* polypeptides of the present invention.

Additional definitions are provided throughout the specification.

Explanation of Table 1

Table 1, below, provides information describing 113 open reading frames (ORFs) which encode potentially antigenic polypeptides of *S. pneumoniae* of the present invention. The table lists the ORF identifier which consists of the letters SP, which denote *S. pneumoniae*, followed immediately by a three digit numeric code, which arbitrarily number the potentially antigenic polypeptides of *S. pneumoniae* of the present invention and the nucleotide or amino acid sequence of each ORF and encoded polypeptide. The table further correlates the ORF identifier with a sequence identification number (SEQ ID NO:). The actual nucleotide or amino acid sequence of each ORF identifier is also shown in the Sequence Listing under the corresponding SEQ ID NO.

Thus, for example, the designation "SP126" refers to both the nucleotide and amino acid sequences of *S. pneumoniae* polypeptide number 126 of the present invention. Further, "SP126" correlates with the nucleotide

8

sequence shown as SEQ ID NO:223 and with the amino acid sequence shown as SEQ ID NO:224 as is described in Table 1.

The open reading frame within each "ORF" begins with the second nucleotide shown. Thus, the first codon for each nucleotide sequence shown is bases 2-4, the second 5-7, the third 8-10, and so on.

Explanation of Table 2

5

10

15

20

25

30

35

Table 2 lists the antigenic epitopes present in each of the S. pneumoniae polypeptides described in Table 1 as predicted by the inventors. Each S. pneumoniae polypeptide shown in Table 1 has one or more antigenic epitopes described in Table 2. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The exact location of the antigenic determinant may shift by about 1 to 5 residues, more likely 1 to 2 residues, depending on the criteria used. Thus, the first antigenic determinant described in Table 2, "Lys-1 to Ile-10" of SP001, represents a peptide comprising the lysine at position 1 in SEQ ID NO:2 through and including the isoleucine at position 10 in SEQ ID NO:2, but may include more or fewer residues than those 10. It will also be appreciated that, generally speaking, amino acids can be added to either terminus of a peptide or polypeptide containing an antigenic epitope without affecting its activity, whereas removing residues from a peptide or polypeptide containing only the antigenic determinant is much more likely to destroy activity. It will be appreciated that the residues and locations shown described in Table 2 correspond to the amino acid sequences for each ORF shown in Table 1 and in the Sequence Listing.

Explanation of Table 3

Table 3 shows PCR primers designed by the inventors for the amplification of polynucleotides encoding polypeptides of the present invention according to the method of Example 1. PCR primer design is routine in the art and those shown in Table 3 are provided merely for the convenience of the skilled artisan. It will be appreciated that others can be used with equal success.

For each primer, the table lists the corresponding ORF designation from Table 1 followed by either an "A" or a "B". The "A" primers are the 5' primers and the "B" primers 3'. A restriction enzyme site was built into each primer to allow ease of cloning. The restriction enzyme which will recognize and cleave a sequence within each primer is shown in Table 3, as well, under the heading

"RE" for restriction enzyme. Finally the sequence identifier is shown in Table 3 for each primer for easy correlation with the Sequence Listing.

Selection of Nucleic Acid Sequences Encoding Antigenic S. pneumoniae Polypeptides

5

10

15

20

25

30

35

The present invention provides a select number of ORFs from those presented in the fragments of the S. pneumoniae genome which may prove useful for the generation of a protective immune response. The sequenced S. pneumoniae genomic DNA was obtained from a sub-cultured isolate of S. pneumoniae Strain 7/87 14.8.91, which has been deposited at the American Type Culture Collection, as a convenience to those of skill in the art. The S. pneumoniae isolate was deposited on October 10, 1996 at the ATCC, 12301 Park Lawn Drive, Rockville, Maryland 20852, and given accession number A genomic library constructed from DNA isolated from the S. pneumoniae isolate was also deposited at the ATCC on October 11, 1996 and given ATCC Deposit No. 97755. A more complete listing of the sequence obtained from the S. pneumoniae genome may be found in co-pending U.S. Provisional Application Serial No. 60/029,960, filed 10/31/96, incorporated herein by reference in its entirety. Some ORFs contained in the subset of fragments of the S. pneumoniae genome disclosed herein were derived through the use of a number of screening criteria detailed below.

The selected ORFs do not consist of complete ORFs. polypeptide representing a complete ORF may be the closest approximation of a protein native to an organism, it is not always preferred to express a complete ORF in a heterologous system. It may be challenging to express and purify a highly hydrophobic protein by common laboratory methods. Thus, the polypeptide vaccine candidates described herein may have been modified slightly to simplify the production of recombinant protein. For example, nucleotide sequences which encode highly hydrophobic domains, such as those found at the amino terminal signal sequence, have been excluded from some constructs used for in vitro expression of the polypeptides. Furthermore, any highly hydrophobic amino acid sequences occurring at the carboxy terminus have also been excluded from the recombinant expression constructs. Thus, in one embodiment, a polypeptide which represents a truncated or modified ORF may be used as an antigen.

While numerous methods are known in the art for selecting potentially immunogenic polypeptides, many of the ORFs disclosed herein were selected

PCT/US97/19422

WO 98/18930

5

10

15

20

25

30

35

on the basis of screening all theoretical *S. pneumoniae* ORFs for several aspects of potential immunogenicity. One set of selection criteria are as follows:

- 1. Type I signal sequence: An amino terminal type I signal sequence generally directs a nascent protein across the plasma and outer membranes to the exterior of the bacterial cell. Experimental evidence obtained from studies with Escherichia coli suggests that the typical type I signal sequence consists of the following biochemical and physical attributes (Izard, J. W. and Kendall, D. A. Mol. Microbiol. 13:765-773 (1994)). The length of the type I signal sequence is approximately 15 to 25 primarily hydrophobic amino acid residues with a net positive charge in the extreme amino terminus. In addition, the central region of the signal sequence adopts an alpha-helical conformation in a hydrophobic environment. Finally, the region surrounding the actual site of cleavage is ideally six residues long, with small side-chain amino acids in the -1 and -3 positions.
- 2. Type IV signal sequence: The type IV signal sequence is an example of the several types of functional signal sequences which exist in addition to the type I signal sequence detailed above. Although functionally related, the type IV signal sequence possesses a unique set of biochemical and physical attributes (Strom, M. S. and Lory, S., J. Bacteriol. 174:7345-7351 (1992)). These are typically six to eight amino acids with a net basic charge followed by an additional sixteen to thirty primarily hydrophobic residues. The cleavage site of a type IV signal sequence is typically after the initial six to eight amino acids at the extreme amino terminus. In addition, type IV signal sequences generally contain a phenylalanine residue at the +1 site relative to the cleavage site.
- 3. Lipoprotein: Studies of the cleavage sites of twenty-six bacterial lipoprotein precursors has allowed the definition of a consensus amino acid sequence for lipoprotein cleavage. Nearly three-fourths of the bacterial lipoprotein precursors examined contained the sequence L-(A,S)-(G,A)-C at positions -3 to +1, relative to the point of cleavage (Hayashi, S. and Wu, H. C., J. Bioenerg. Biomembr. 22:451-471 (1990)).
- 4. LPXTG motif: It has been experimentally determined that most anchored proteins found on the surface of gram-positive bacteria possess a highly conserved carboxy terminal sequence. More than fifty such proteins from organisms such as S. pyogenes, S. mutans, E. faecalis, S. pneumoniae, and others, have been identified based on their extracellular location and carboxy terminal amino acid sequence (Fischetti, V. A., ASM News 62:405-410 (1996)). The conserved region consists of six charged amino acids at the extreme carboxy terminus coupled to 15-20 hydrophobic amino acids

11

presumed to function as a transmembrane domain. Immediately adjacent to the transmembrane domain is a six amino acid sequence conserved in nearly all proteins examined. The amino acid sequence of this region is L-P-X-T-G-X, where X is any amino acid.

An algorithm for selecting antigenic and immunogenic *S. pneumoniae* polypeptides including the foregoing criteria was developed. Use of the algorithm by the inventors to select immunologically useful *S. pneumoniae* polypeptides resulted in the selection of a number of the disclosed ORFs. Polypeptides comprising the polypeptides identified in this group may be produced by techniques standard in the art and as further described herein.

Nucleic Acid Molecules

5

10

15

20

25

30

35

The present invention provides isolated nucleic acid molecules comprising polynucleotides encoding the *S. pneumoniae* polypeptides having the amino acid sequences described in Table 1 and shown as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and so on through SEQ ID NO:226, which were determined by sequencing the genome of *S. pneumoniae* and selected as putative immunogens.

Unless otherwise indicated, all nucleotide sequences determined by sequencing a DNA molecule herein were determined using an automated DNA sequencer (such as the Model 373 from Applied Biosystems, Inc.), and all amino acid sequences of polypeptides encoded by DNA molecules determined herein were predicted by translation of DNA sequences determined as above. Therefore, as is known in the art for any DNA sequence determined by this automated approach, any nucleotide sequence determined herein may contain some errors. Nucleotide sequences determined by automation are typically at least about 90% identical, more typically at least about 95% to at least about 99.9% identical to the actual nucleotide sequence of the sequenced DNA molecule. The actual sequence can be more precisely determined by other approaches including manual DNA sequencing methods well known in the art. As is also known in the art, a single insertion or deletion in a determined nucleotide sequence compared to the actual sequence will cause a frame shift in translation of the nucleotide sequence such that the predicted amino acid sequence encoded by a determined nucleotide sequence will be completely different from the amino acid sequence actually encoded by the sequenced DNA molecule, beginning at the point of such an insertion or deletion.

Unless otherwise indicated, each "nucleotide sequence" set forth herein is presented as a sequence of deoxyribonucleotides (abbreviated A, G, C and

PCT/US97/19422

5

10

15

20

25

30

35

T). However, by "nucleotide sequence" of a nucleic acid molecule or polynucleotide is intended, for a DNA molecule or polynucleotide, a sequence of deoxyribonucleotides, and for an RNA molecule or polynucleotide, the corresponding sequence of ribonucleotides (A, G, C and U), where each thymidine deoxyribonucleotide (T) in the specified deoxyribonucleotide sequence is replaced by the ribonucleotide uridine (U). For instance, reference to an RNA molecule having a sequence described in Table 1 set forth using deoxyribonucleotide abbreviations is intended to indicate an RNA molecule having a sequence in which each deoxyribonucleotide A, G or C described in Table 1 has been replaced by the corresponding ribonucleotide A, G or C, and each deoxyribonucleotide T has been replaced by a ribonucleotide U.

Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced synthetically. The DNA may be double-stranded or single-stranded. Single-stranded DNA or RNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand.

By "isolated" nucleic acid molecule(s) is intended a nucleic acid molecule, DNA or RNA, which has been removed from its native environment. For example, recombinant DNA molecules contained in a vector are considered isolated for the purposes of the present invention. Further examples of isolated DNA molecules include recombinant DNA molecules maintained in heterologous host cells or purified (partially or substantially) DNA molecules in solution. Isolated RNA molecules include *in vivo* or *in vitro* RNA transcripts of the DNA molecules of the present invention. Isolated nucleic acid molecules according to the present invention further include such molecules produced synthetically.

Isolated nucleic acid molecules of the present invention include DNA molecules comprising a nucleotide sequence described in Table 1 and shown as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, and so on through SEQ ID NO:225; DNA molecules comprising the coding sequences for the polypeptides described in Table 1 and shown as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and so on through SEQ ID NO:226; and DNA molecules which comprise sequences substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the *S. pneumoniae* polypeptides described in Table 1. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate variants.

The invention also provides nucleic acid molecules having sequences complementary to any one of those described in Table 1. Such isolated molecules, particularly DNA molecules, are useful as probes for detecting expression of *Streptococcal* genes, for instance, by Northern blot analysis or the polymerase chain reaction (PCR).

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated nucleic acid molecule having a nucleotide sequence described in Table 1, is intended fragments at least about 15 nt, and more preferably at least about 17 nt, still more preferably at least about 20 nt, and even more preferably, at least about 25 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-100 nt in length are also useful according to the present invention as are fragments corresponding to most, if not all, of a nucleotide sequence described in Table 1. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases of a nucleotide sequence as described in Table 1. Since the nucleotide sequences identified in Table 1 are provided as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, and so on through SEQ ID NO:225, generating such DNA fragments would be routine to the skilled artisan. For example, such fragments could be generated synthetically.

Preferred nucleic acid fragments of the present invention also include nucleic acid molecules comprising nucleotide sequences encoding epitope-bearing portions of the *S. pneumoniae* polypeptides identified in Table 1. Such nucleic acid fragments of the present invention include, for example, nucleotide sequences encoding polypeptide fragments comprising from about the amino terminal residue to about the carboxy terminal residue of each fragment shown in Table 2. The above referred to polypeptide fragments are antigenic regions of the *S. pneumoniae* polypeptides identified in Table 1.

In another aspect, the invention provides isolated nucleic acid molecules comprising polynucleotides which hybridize under stringent hybridization conditions to a portion of a polynucleotide in a nucleic acid molecule of the invention described above, for instance, a nucleic acid sequence identified in Table 1. By "stringent hybridization conditions" is intended overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (150 mM NaCl, 15 mM trisodium citrate). 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 g/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65°C.

By polynucleotides which hybridize to a "portion" of a polynucleotide is intended polynucleotides (either DNA or RNA) which hybridize to at least about 15 nucleotides (nt), and more preferably at least about 17 nt, still more preferably at least about 20 nt, and even more preferably about 25-70 nt of the reference polynucleotide. These are useful as diagnostic probes and primers as discussed above and in more detail below.

Of course, polynucleotides hybridizing to a larger portion of the reference polynucleotide, for instance, a portion 50-100 nt in length, or even to the entire length of the reference polynucleotide, are also useful as probes according to the present invention, as are polynucleotides corresponding to most, if not all, of a nucleotide sequence as identified in Table 1. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., a nucleotide sequences as described in Table 1). As noted above, such portions are useful diagnostically either as probes according to conventional DNA hybridization techniques or as primers for amplification of a target sequence by PCR, as described in the literature (for instance, in Molecular Cloning, A Laboratory Manual, 2nd. edition, Sambrook, J., Fritsch, E. F. and Maniatis, T., eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), the entire disclosure of which is hereby incorporated herein by reference).

Since nucleic acid sequences encoding the *S. pneumoniae* polypeptides of the present invention are identified in Table 1 and provided as SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, and so on through SEQ ID NO:225, generating polynucleotides which hybridize to portions of these sequences would be routine to the skilled artisan. For example, the hybridizing polynucleotides of the present invention could be generated synthetically according to known techniques.

As indicated, nucleic acid molecules of the present invention which encode *S. pneumoniae* polypeptides of the present invention may include, but are not limited to those encoding the amino acid sequences of the polypeptides by themselves; and additional coding sequences which code for additional amino acids, such as those which provide additional functionalities. Thus, the sequences encoding these polypeptides may be fused to a marker sequence, such as a sequence encoding a peptide which facilitates purification of the fused polypeptide. In certain preferred embodiments of this aspect of the invention, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (Qiagen, Inc.), among others, many of which are

commercially available. As described by Gentz and colleagues (*Proc. Natl. Acad. Sci. USA* 86:821-824 (1989)), for instance, hexa-histidine provides for convenient purification of the resulting fusion protein.

5

10

15

20

25

30

35

Thus, the present invention also includes genetic fusions wherein the *S. pneumoniae* nucleic acid sequences coding sequences identified in Table 1 are linked to additional nucleic acid sequences to produce fusion proteins. These fusion proteins may include epitopes of streptococcal or non-streptococcal origin designed to produce proteins having enhanced immunogenicity. Further, the fusion proteins of the present invention may contain antigenic determinants known to provide helper T-cell stimulation, peptides encoding sites for post-translational modifications which enhance immunogenicity (*e.g.*, acylation), peptides which facilitate purification (*e.g.*, histidine "tag"), or amino acid sequences which target the fusion protein to a desired location (*e.g.*, a heterologous leader sequence).

In all cases of bacterial expression, an N-terminal methionine residues is added. In many cases, however, the N-terminal methionine residues is cleaved off post-translationally. Thus, the invention includes polypeptides shown in Table 1 with, and without an N-termainal methionine.

The present invention thus includes nucleic acid molecules and sequences which encode fusion proteins comprising one or more S. pneumoniae polypeptides of the present invention fused to an amino acid sequence which allows for post-translational modification to enhance immunogenicity. This post-translational modification may occur either in vitro or when the fusion protein is expressed in vivo in a host cell. An example of such a modification is the introduction of an amino acid sequence which results in the attachment of a lipid moiety.

Thus, as indicated above, the present invention includes genetic fusions wherein a S. pneumoniae nucleic acid sequence identified in Table 1 is linked to a nucleotide sequence encoding another amino acid sequence. These other amino acid sequences may be of streptococcal origin (e.g., another sequence selected from Table 1) or non-streptococcal origin.

The present invention further relates to variants of the nucleic acid molecules of the present invention, which encode portions, analogs or derivatives of the *S. pneumoniae* polypeptides described in Table 1. Variants may occur naturally, such as a natural allelic variant. By an "allelic variant" is intended one of several alternate forms of a gene occupying a given locus on a chromosome of an organism (*Genes II*, Lewin, B., ed., John Wiley & Sons,

16

New York (1985)). Non-naturally occurring variants may be produced using art-known mutagenesis techniques.

Such variants include those produced by nucleotide substitutions, deletions or additions. The substitutions, deletions or additions may involve one or more nucleotides. These variants may be altered in coding regions, non-coding regions, or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the *S. pneumoniae* polypeptides disclosed herein or portions thereof. Silent substitution are most likely to be made in non-epitopic regions. Guidance regarding those regions containing epitopes is provided herein, for example, in Table 2. Also especially preferred in this regard are conservative substitutions.

5

10

15

20

25

30

35

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 90% identical, and more preferably at least 95%, 96%, 97%, 98% or 99% identical to: (a) a nucleotide sequence encoding any of the amino acid sequences of the polypeptides identified in Table 1; and (b) a nucleotide sequence complementary to any of the nucleotide sequences in (a) above.

By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence encoding a S. pneumoniae polypeptide described in Table 1, is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the subject S. pneumoniae polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. These mutations of the reference sequence may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence.

Certain nucleotides within some of the nucleic acid sequences shown in Table 1 were ambiguous upon sequencing. Completely unknown sequences are shown as an "N". Other unresolved nucleotides are known to be either a

17

purine, shown as "R", or a pyrimidine, shown as "Y". Accordingly, when determining identity between two nucleotide sequences, identity is met where any nucleotide, including an "R", "Y" or "N", is found in a test sequence and at the corresponding position in the referece sequence (from Table 1). Likewise, an A, G or "R" in a test sequence is identical to an "R" in the reference sequence; and a T, C or "Y" in a test sequence is identical to a "Y" in the reference sequence.

5

10

15

20

25

30

35

As a practical matter, whether any particular nucleic acid molecule is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, a nucleotide sequence described in Table 1 can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). Bestfit uses the local homology algorithm of Smith and Waterman (*Advances in Applied Mathematics* 2:482-489 (1981)), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleic acid sequences described in Table 1. One of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention include, *inter alia*, (1) isolating *Streptococcal* genes or allelic variants thereof from either a genomic or cDNA library and (2) Northern Blot or PCR analysis for detecting *Streptococcal* mRNA expression.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of nucleic acid molecules having a sequence at least 90%, 95%, 96%, 97%, 98%, or 99% identical to a nucleic acid sequence identified in Table 1 will encode the same polypeptide. In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay.

It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode

proteins having antigenic epitopes of the *S. pneumoniae* polypeptides of the present invention. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect the antigenicity of a polypeptide (e.g., replacement of an amino acid in a region which is not believed to form an antigenic epitope). For example, since antigenic epitopes have been identified which contain as few as six amino acids (see Harlow, et al., Antibodies: A Laboratory Manual, 2nd Ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1988), page 76), in instances where a polypeptide has multiple antigenic epitopes the alteration of several amino acid residues would often not be expected to eliminate all of the antigenic epitopes of that polypeptide. This is especially so when the alterations are in regions believed to not constitute antigenic epitopes.

Vectors and Host Cells

15

5

10

The present invention also relates to vectors which include the isolated DNA molecules of the present invention, host cells which are genetically engineered with the recombinant vectors, and the production of *S. pneumoniae* polypeptides or fragments thereof by recombinant techniques.

20

Recombinant constructs may be introduced into host cells using well known techniques such as infection, transduction, transfection, transvection, electroporation and transformation. The vector may be, for example, a phage, plasmid, viral or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

25

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

30

Preferred are vectors comprising *cis*-acting control regions to the polynucleotide of interest. Appropriate *trans*-acting factors may be supplied by the host, supplied by a complementing vector or supplied by the vector itself upon introduction into the host.

35

In certain preferred embodiments in this regard, the vectors provide for specific expression, which may be inducible and/or cell type-specific. Particularly preferred among such vectors are those inducible by environmental factors that are easy to manipulate, such as temperature and nutrient additives.

19

Expression vectors useful in the present invention include chromosomal-, episomal- and virus-derived vectors, e.g., vectors derived from bacterial plasmids, bacteriophage, yeast episomes, yeast chromosomal elements, viruses such as baculoviruses, papova viruses, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as cosmids and phagemids.

5

10

15

20

25

30

35

The DNA insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating site at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase or neomycin resistance for eukaryotic cell culture and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells: fungal cells, such as yeast cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from Qiagen; pBS vectors, Phagescript vectors, Bluescript vectors, pNH8A, pNH16a, pNH18A, pNH46A available from Stratagene; pET series of vectors available from Novagen: and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Among known bacterial promoters suitable for use in the present invention include the *E. coli lac*I and *lac*Z promoters, the T3 and T7 promoters, the *gpt* promoter, the lambda PR and PL promoters and the *trp* promoter. Suitable eukaryotic promoters include the CMV immediate early promoter, the

HSV thymidine kinase promoter, the early and late SV40 promoters, the promoters of retroviral LTRs, such as those of the Rous sarcoma virus (RSV), and metallothionein promoters, such as the mouse metallothionein-I promoter.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other methods. Such methods are described in many standard laboratory manuals (for example, Davis, et al., Basic Methods In Molecular Biology (1986)).

5

10

15

20

25

30

35

Transcription of DNA encoding the polypeptides of the present invention by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are *cis*-acting elements of DNA, usually about from 10 to 300 bp that act to increase transcriptional activity of a promoter in a given host cell-type. Examples of enhancers include the SV40 enhancer, which is located on the late side of the replication origin at bp 100 to 270, the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

For secretion of the translated polypeptide into the lumen of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into the expressed polypeptide. The signals may be endogenous to the polypeptide or they may be heterologous signals.

The polypeptide may be expressed in a modified form, such as a fusion protein, and may include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability and to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize proteins. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is thoroughly advantageous for use in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262).

21

On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified in the advantageous manner described. This is the case when Fc portion proves to be a hindrance to use in therapy and diagnosis, for example when the fusion protein is to be used as antigen for immunizations. In drug discovery, for example, human proteins, such as, hIL5-receptor has been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See Bennett, D. et al., J. Molec. Recogn. 8:52-58 (1995) and Johanson, K. et al., J. Biol. Chem. 270 (16):9459-9471 (1995).

The *S. pneumoniae* polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography, lectin chromatography and high performance liquid chromatography ("HPLC") is employed for purification. Polypeptides of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells.

Polypeptides and Fragments

5

10

15

20

25

30

35

The invention further provides isolated polypeptides having the amino acid sequences described in Table 1, and shown as SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and so on through SEQ ID NO:226, and peptides or polypeptides comprising portions of the above polypeptides. The terms "peptide" and "oligopeptide" are considered synonymous (as is commonly recognized) and each term can be used interchangeably as the context requires to indicate a chain of at least two amino acids coupled by peptidyl linkages. The word "polypeptide" is used herein for chains containing more than ten amino acid residues. All oligopeptide and polypeptide formulas or sequences herein are written from left to right and in the direction from amino terminus to carboxy terminus.

Some amino acid sequences of the *S. pneumoniae* polypeptides described in Table 1 can be varied without significantly effecting the antigenicity of the polypeptides. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine antigenicity. In general, it is possible to replace residues which do

22

not form part of an antigenic epitope without significantly effecting the antigenicity of a polypeptide. Guidance for such alterations is given in Table 2 wherein epitopes for each polypeptide is delineated.

The polypeptides of the present invention are preferably provided in an isolated form. By "isolated polypeptide" is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and/or contained within a recombinant host cell is considered isolated for purposes of the present invention. Also intended as an "isolated polypeptide" is a polypeptide that has been purified, partially or substantially, from a recombinant host cell. For example, recombinantly produced versions of the *S. pneumoniae* polypeptides described in Table 1 can be substantially purified by the one-step method described by Smith and Johnson (*Gene* 67:31-40 (1988)).

5

10

15

20

25

30

35

The polypeptides of the present invention include: (a) an amino acid sequence of any of the polypeptides described in Table 1; and (b) an amino acid sequence of an epitope-bearing portion of any one of the polypeptides of (a); as well as polypeptides with at least 70% similarity, and more preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% similarity to those described in (a) or (b) above, as well as polypeptides having an amino acid sequence at least 70% identical, more preferably at least 75% identical, and still more preferably 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to those above.

By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489 (1981)) to find the best segment of similarity between two sequences.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a *S. pneumoniae* polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to

23

5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

5

10

15

20

25

30

35

The amino acid sequences shown in Table 1 may have on or more "X" residues. "X" represents unknown. Thus, for purposes of defining identity, if any amino acid is present at the same position in a reference amino acid sequence (shown in Table 1) where an X is shown, the two sequences are identical at that position.

As a practical matter, whether any particular polypeptide is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to, for instance, an amino acid sequence shown in Table 1, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

As described below, the polypeptides of the present invention can also be used to raise polyclonal and monoclonal antibodies, which are useful in assays for detecting *Streptococcal* protein expression.

In another aspect, the invention provides peptides and polypeptides comprising epitope-bearing portions of the *S. pneumoniae* polypeptides of the invention. These epitopes are immunogenic or antigenic epitopes of the polypeptides of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein or polypeptide is the immunogen. These immunogenic epitopes are believed to be confined to a few loci on the molecule. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic determinant" or "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes (Geysen, *et al.*, *Proc. Natl. Acad. Sci. USA* 81:3998- 4002 (1983)). Predicted antigenic epitopes are shown in Table 2, below.

WO 98/18930

5

10

15

20

25

30

35

As to the selection of peptides or polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein (for instance, Sutcliffe, J., et al., Science 219:660-666 (1983)). Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Peptides that are extremely hydrophobic and those of six or fewer residues generally are ineffective at inducing antibodies that bind to the mimicked protein; longer, peptides, especially those containing proline residues, usually are effective (Sutcliffe, et al., supra, p. 661). For instance, 18 of 20 peptides designed according to these guidelines, containing 8-39 residues covering 75% of the sequence of the influenza virus hemagglutinin HA1 polypeptide chain, induced antibodies that reacted with the HA1 protein or intact virus; and 12/12 peptides from the MuLV polymerase and 18/18 from the rabies glycoprotein induced antibodies that precipitated the respective proteins.

24

PCT/US97/19422

Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. Thus, a high proportion of hybridomas obtained by fusion of spleen cells from donors immunized with an antigen epitope-bearing peptide generally secrete antibody reactive with the native protein (Sutcliffe, et al., supra, p. 663). The antibodies raised by antigenic epitope-bearing peptides or polypeptides are useful to detect the mimicked protein, and antibodies to different peptides may be used for tracking the fate of various regions of a protein precursor which undergoes post-translational processing. The peptides and anti-peptide antibodies may be used in a variety of qualitative or quantitative assays for the mimicked protein, for instance in competition assays since it has been shown that even short peptides (e.g., about 9 amino acids) can bind and displace the larger peptides in immunoprecipitation assays (for instance, Wilson, et al., Cell 37:767-778 (1984) p. 777). The anti-peptide antibodies of the invention also are useful for purification of the mimicked protein, for instance, by chromatography using methods well known in the art.

Antigenic epitope-bearing peptides and polypeptides of the invention designed according to the above guidelines preferably contain a sequence of at

least seven, more preferably at least nine and most preferably between about 15 to about 30 amino acids contained within the amino acid sequence of a polypeptide of the invention. However, peptides or polypeptides comprising a larger portion of an amino acid sequence of a polypeptide of the invention, containing about 30 to about 50 amino acids, or any length up to and including the entire amino acid sequence of a polypeptide of the invention, also are considered epitope-bearing peptides or polypeptides of the invention and also are useful for inducing antibodies that react with the mimicked protein. Preferably, the amino acid sequence of the epitope-bearing peptide is selected to provide substantial solubility in aqueous solvents (*i.e.*, the sequence includes relatively hydrophilic residues and highly hydrophobic sequences are preferably avoided); and sequences containing proline residues are particularly preferred.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate *Streptococcal*-specific antibodies include portions of the amino acid sequences identified in Table 1. More specifically, Table 2 discloses antigenic fragments of polypeptides of the present invention, which antigenic fragments comprise amino acid sequences from about the first amino acid residues indicated to about the last amino acid residue indicated for each fragment. The polypeptide fragments disclosed in Table 2 are believed to be antigenic regions of the *S. pneumoniae* polypeptides described in Table 1. Thus the invention further includes isolated peptides and polypeptides comprising an amino acid sequence of an epitope shown in Table 2 and polynucleotides encoding said polypeptides.

The epitope-bearing peptides and polypeptides of the invention may be produced by any conventional means for making peptides or polypeptides including recombinant means using nucleic acid molecules of the invention. For instance, an epitope-bearing amino acid sequence of the present invention may be fused to a larger polypeptide which acts as a carrier during recombinant production and purification, as well as during immunization to produce anti-peptide antibodies. Epitope-bearing peptides also may be synthesized using known methods of chemical synthesis. For instance, Houghten has described a simple method for synthesis of large numbers of peptides, such as 10-20 mg of 248 different 13 residue peptides representing single amino acid variants of a segment of the HA1 polypeptide which were prepared and characterized (by ELISA-type binding studies) in less than four weeks (Houghten, R. A. Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985)). This "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Patent No. 4,631,211 to Houghten and coworkers (1986). In this procedure the individual

26

resins for the solid-phase synthesis of various peptides are contained in separate solvent-permeable packets, enabling the optimal use of the many identical repetitive steps involved in solid-phase methods. A completely manual procedure allows 500-1000 or more syntheses to be conducted simultaneously (Houghten, et al., supra, p. 5134).

5

10

15

20

25

30

35

Epitope-bearing peptides and polypeptides of the invention are used to induce antibodies according to methods well known in the art (for instance, Sutcliffe, et al., supra; Wilson, et al., supra; Chow, M., et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J., et al., J. Gen. Virol. 66:2347-2354 (1985)). Generally, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling of the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine may be coupled to carrier using a linker such as m-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carrier using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg peptide or carrier protein and Freund's adjuvant. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

Immunogenic epitope-bearing peptides of the invention, *i.e.*, those parts of a protein that elicit an antibody response when the whole protein is the immunogen, are identified according to methods known in the art. For instance, Geysen, *et al.*, *supra*, discloses a procedure for rapid concurrent synthesis on solid supports of hundreds of peptides of sufficient purity to react in an enzyme-linked immunosorbent assay. Interaction of synthesized peptides with antibodies is then easily detected without removing them from the support. In this manner a peptide bearing an immunogenic epitope of a desired protein may be identified routinely by one of ordinary skill in the art. For instance, the immunologically important epitope in the coat protein of foot-and-mouth disease virus was located by Geysen *et al. supra* with a resolution of seven amino acids by synthesis of an overlapping set of all 208 possible hexapeptides covering the

entire 213 amino acid sequence of the protein. Then, a complete replacement set of peptides in which all 20 amino acids were substituted in turn at every position within the epitope were synthesized, and the particular amino acids conferring specificity for the reaction with antibody were determined. Thus, peptide analogs of the epitope-bearing peptides of the invention can be made routinely by this method. U.S. Patent No. 4,708,781 to Geysen (1987) further describes this method of identifying a peptide bearing an immunogenic epitope of a desired protein.

Further still, U.S. Patent No. 5,194,392, to Geysen (1990), describes a general method of detecting or determining the sequence of monomers (amino acids or other compounds) which is a topological equivalent of the epitope (*i.e.*, a "mimotope") which is complementary to a particular paratope (antigen binding site) of an antibody of interest. More generally, U.S. Patent No. 4,433,092, also to Geysen (1989), describes a method of detecting or determining a sequence of monomers which is a topographical equivalent of a ligand which is complementary to the ligand binding site of a particular receptor of interest. Similarly, U.S. Patent No. 5,480,971 to Houghten, R. A. *et al.* (1996) discloses linear C₁-C₇-alkyl peralkylated oligopeptides and sets and libraries of such peptides, as well as methods for using such oligopeptide sets and libraries for determining the sequence of a peralkylated oligopeptide that preferentially binds to an acceptor molecule of interest. Thus, non-peptide analogs of the epitope-bearing peptides of the invention also can be made routinely by these methods.

The entire disclosure of each document cited in this section on "Polypeptides and Fragments" is hereby incorporated herein by reference.

As one of skill in the art will appreciate, the polypeptides of the present invention and the epitope-bearing fragments thereof described above can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. This has been shown, e.g., for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins (EPA 0,394,827; Traunecker et al., Nature 331:84-86 (1988)). Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than a monomeric S. pneumoniae polypeptide or

28

fragment thereof alone (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)).

Diagnostic Assays

5

10

15

The present invention further relates to a method for assaying for Streptococcal infection in an animal via detecting the expression of genes encoding Streptococcal polypeptides (e.g., the polypeptides described Table 1). This method comprises analyzing tissue or body fluid from the animal for Streptococcus-specific antibodies or Streptococcus can be done by PCR or hybridization techniques using nucleic acid sequences of the present invention as either hybridization probes or primers (cf. Molecular Cloning: A Laboratory Manual, second edition, edited by Sambrook, Fritsch, & Maniatis, Cold Spring Harbor Laboratory, 1989; Eremeeva et al., J. Clin. Microbiol. 32:803-810 (1994) which describes differentiation among spotted fever group Rickettsiae species by analysis of restriction fragment length polymorphism of PCR-amplified DNA). Methods for detecting B. burgdorferi nucleic acids via PCR are described, for example, in Chen et al., J. Clin. Microbiol. 32:589-595 (1994).

20

Where diagnosis of a disease state related to infection with *Streptococcus* has already been made, the present invention is useful for monitoring progression or regression of the disease state whereby patients exhibiting enhanced *Streptococcus* gene expression will experience a worse clinical outcome relative to patients expressing these gene(s) at a lower level.

25

30

35

By "assaying for Streptococcal infection in an animal via detection of genes encoding Streptococcal polypeptides" is intended qualitatively or quantitatively measuring or estimating the level of one or more Streptococcus polypeptides or the level of nucleic acid encoding Streptococcus polypeptides in a first biological sample either directly (e.g., by determining or estimating absolute protein level or nucleic level) or relatively (e.g., by comparing to the Streptococcus polypeptide level or mRNA level in a second biological sample). The Streptococcus polypeptide level or nucleic acid level in the second sample used for a relative comparison may be undetectable if obtained from an animal which is not infected with Streptococcus. When monitoring the progression or regression of a disease state, the Streptococcus polypeptide level or nucleic acid level may be compared to a second sample obtained from either an animal infected with Streptococcus or the same animal from which the first sample was obtained but taken from that animal at a different time than the first. As will be

appreciated in the art, once a standard *Streptococcus* polypeptide level or nucleic acid level which corresponds to a particular stage of a *Streptococcus* infection is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an animal, cell line, tissue culture, or other source which contains *Streptococcus* polypeptide, mRNA, or DNA. Biological samples include body fluids (such as plasma and synovial fluid) which contain *Streptococcus* polypeptides, and muscle, skin, and cartilage tissues. Methods for obtaining tissue biopsies and body fluids are well known in the art.

5

10

15

20

25

30

35 .

The present invention is useful for detecting diseases related to *Streptococcus* infections in animals. Preferred animals include monkeys, apes, cats, dogs, cows, pigs, mice, horses, rabbits and humans. Particularly preferred are humans.

Total RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, *Anal. Biochem. 162:*156-159 (1987). mRNA encoding *Streptococcus* polypeptides having sufficient homology to the nucleic acid sequences identified in Table 1 to allow for hybridization between complementary sequences are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

Northern blot analysis can be performed as described in Harada *et al.*, *Cell 63:*303-312 (1990). Briefly, total RNA is prepared from a biological sample as described above. For the Northern blot, the RNA is denatured in an appropriate buffer (such as glyoxal/dimethyl sulfoxide/sodium phosphate buffer), subjected to agarose gel electrophoresis, and transferred onto a nitrocellulose filter. After the RNAs have been linked to the filter by a UV linker, the filter is prehybridized in a solution containing formamide, SSC, Denhardt's solution, denatured salmon sperm, SDS, and sodium phosphate buffer. A *S. pnuemoniae* polypeptide DNA sequence shown in Table 1 labeled according to any appropriate method (such as the ³²P-multiprimed DNA labeling system (Amersham)) is used as probe. After hybridization overnight, the filter is washed and exposed to x-ray film. DNA for use as probe according to the present invention is described in the sections above and will preferably at least 15 bp in length.

30

S1 mapping can be performed as described in Fujita et al., Cell 49:357-367 (1987). To prepare probe DNA for use in S1 mapping, the sense strand of an above-described S. pnuemoniae DNA sequence of the present invention is used as a template to synthesize labeled antisense DNA. The antisense DNA can then be digested using an appropriate restriction endonuclease to generate further DNA probes of a desired length. Such antisense probes are useful for visualizing protected bands corresponding to the target mRNA (i.e., mRNA encoding Streptococcus polypeptides).

5

10

15

20

25

30

35

Preferably, levels of mRNA encoding Streptococcus polypeptides are assayed using the RT-PCR method described in Makino et al., Technique 2:295-301 (1990). By this method, the radioactivities of the "amplicons" in the polyacrylamide gel bands are linearly related to the initial concentration of the target mRNA. Briefly, this method involves adding total RNA isolated from a biological sample in a reaction mixture containing a RT primer and appropriate buffer. After incubating for primer annealing, the mixture can be supplemented with a RT buffer, dNTPs, DTT, RNase inhibitor and reverse transcriptase. After incubation to achieve reverse transcription of the RNA, the RT products are then subject to PCR using labeled primers. Alternatively, rather than labeling the primers, a labeled dNTP can be included in the PCR reaction mixture. PCR amplification can be performed in a DNA thermal cycler according to conventional techniques. After a suitable number of rounds to achieve amplification, the PCR reaction mixture is electrophoresed on a polyacrylamide gel. After drying the gel, the radioactivity of the appropriate bands (corresponding to the mRNA encoding the Streptococcus polypeptides)) is quantified using an imaging analyzer. RT and PCR reaction ingredients and conditions, reagent and gel concentrations, and labeling methods are well known in the art. Variations on the RT-PCR method will be apparent to the skilled artisan.

Assaying *Streptococcus* polypeptide levels in a biological sample can occur using any art-known method. Preferred for assaying *Streptococcus* polypeptide levels in a biological sample are antibody-based techniques. For example, *Streptococcus* polypeptide expression in tissues can be studied with classical immunohistological methods. In these, the specific recognition is provided by the primary antibody (polyclonal or monoclonal) but the secondary detection system can utilize fluorescent, enzyme, or other conjugated secondary antibodies. As a result, an immunohistological staining of tissue section for pathological examination is obtained. Tissues can also be extracted, *e.g.*, with urea and neutral detergent, for the liberation of *Streptococcus* polypeptides for

31

Western-blot or dot/slot assay (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987)). In this technique, which is based on the use of cationic solid phases, quantitation of a Streptococcus polypeptide can be accomplished using an isolated Streptococcus polypeptide as a standard. This technique can also be applied to body fluids.

5

10

15

20

25

30

35

Other antibody-based methods useful for detecting *Streptococcus* polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). For example, a *Streptococcus* polypeptide-specific monoclonal antibodies can be used both as an immunoabsorbent and as an enzyme-labeled probe to detect and quantify a *Streptococcus* polypeptide. The amount of a *Streptococcus* polypeptide present in the sample can be calculated by reference to the amount present in a standard preparation using a linear regression computer algorithm. Such an ELISA for detecting a tumor antigen is described in Iacobelli *et al.*, *Breast Cancer Research and Treatment 11:*19-30 (1988). In another ELISA assay, two distinct specific monoclonal antibodies can be used to detect *Streptococcus* polypeptides in a body fluid. In this assay, one of the antibodies is used as the immunoabsorbent and the other as the enzyme-labeled probe.

The above techniques may be conducted essentially as a "one-step" or "two-step" assay. The "one-step" assay involves contacting the *Streptococcus* polypeptide with immobilized antibody and, without washing, contacting the mixture with the labeled antibody. The "two-step" assay involves washing before contacting the mixture with the labeled antibody. Other conventional methods may also be employed as suitable. It is usually desirable to immobilize one component of the assay system on a support, thereby allowing other components of the system to be brought into contact with the component and readily removed from the sample.

· .

Streptococcus polypeptide-specific antibodies for use in the present invention can be raised against an intact S. pneumoize polypeptide of the present invention or fragment thereof. These polypeptides and fragments may be administered to an animal (e,g), rabbit or mouse) either with a carrier protein (e,g), albumin) or, if long enough (e,g), at least about 25 amino acids), without a carrier.

As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')₂ fragments) which are capable of specifically binding to a *Streptococcus* polypeptide. Fab and F(ab')₂ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may

PCT/US97/19422 WO 98/18930

have less non-specific tissue binding of an intact antibody (Wahl et al., J. Nucl. Med. 24:316-325 (1983)). Thus, these fragments are preferred.

The antibodies of the present invention may be prepared by any of a variety of methods. For example, the S. pneumoniae polypeptides identified in Table 1, or fragments thereof, can be administered to an animal in order to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of a S. pneumoniae polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of high specific activity.

5

10

15

20

25

30

35

In the most preferred method, the antibodies of the present invention are monoclonal antibodies. Such monoclonal antibodies can be prepared using hybridoma technology (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., In: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., (1981) pp. 563-681). In general, such procedures involve immunizing an animal (preferably a mouse) with a S. pneumoniae polypeptide antigen of the present invention. Suitable cells can be recognized by their capacity to bind anti-Streptococcus polypeptide antibody. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1.000 U/ml of penicillin, and about 100 µg/ml of streptomycin. The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the American Type Culture Collection, Rockville, Maryland. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the Streptococcus polypeptide antigen administered to immunized animal.

Alternatively, additional antibodies capable of binding to Streptococcus polypeptide antigens may be produced in a two-step procedure through the use of anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and that, therefore, it is possible to obtain an antibody

33

which binds to a second antibody. In accordance with this method, *Streptococcus* polypeptide-specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the *Streptococcus* polypeptide-specific antibody can be blocked by a *Streptococcus* polypeptide antigen. Such antibodies comprise anti-idiotypic antibodies to the *Streptococcus* polypeptide-specific antibody and can be used to immunize an animal to induce formation of further *Streptococcus* polypeptide-specific antibodies.

5

10

15

20

25

30

35

It will be appreciated that Fab and $F(ab')_2$ and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce $F(ab')_2$ fragments). Alternatively, *Streptococcus* polypeptide-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

Of special interest to the present invention are antibodies to Streptococcus polypeptide antigens which are produced in humans, or are "humanized" (i.e., non-immunogenic in a human) by recombinant or other technology. Humanized antibodies may be produced, for example by replacing an immunogenic portion of an antibody with a corresponding, but nonimmunogenic portion (i.e., chimeric antibodies) (Robinson, R.R. et al., International Patent Publication PCT/US86/02269; Akira, K. et al., European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison, S.L. et al., European Patent Application 173,494; Neuberger, M.S. et al., PCT Application WO 86/01533; Cabilly, S. et al., European Patent Application 125,023; Better, M. et al., Science 240:1041-1043 (1988); Liu, A.Y. et al., Proc. Natl. Acad. Sci. USA 84:3439-3443 (1987); Liu, A.Y. et al., J. Immunol. 139:3521-3526 (1987); Sun, L.K. et al., Proc. Natl. Acad. Sci. USA 84:214-218 (1987); Nishimura, Y. et al., Canc. Res. 47:999-1005 (1987); Wood, C.R. et al., Nature 314:446-449 (1985)); Shaw et al., J. Natl. Cancer Inst. 80:1553-1559 (1988). General reviews of "humanized" chimeric antibodies are provided by Morrison, S.L. (Science, 229:1202-1207 (1985)) and by Oi, V.T. et al., BioTechniques 4:214 (1986)). Suitable "humanized" antibodies can be alternatively produced by CDR or CEA substitution (Jones, P.T. et al., Nature 321:552-525 (1986);

34

Verhoeyan et al., Science 239:1534 (1988); Beidler, C.B. et al., J. Immunol. 141:4053-4060 (1988)).

Suitable enzyme labels include, for example, those from the oxidase group, which catalyze the production of hydrogen peroxide by reacting with substrate. Glucose oxidase is particularly preferred as it has good stability and its substrate (glucose) is readily available. Activity of an oxidase label may be assayed by measuring the concentration of hydrogen peroxide formed by the enzyme-labeled antibody/substrate reaction. Besides enzymes, other suitable labels include radioisotopes, such as iodine (¹²⁵I, ¹²¹I), carbon (¹⁴C), sulphur (³⁵S), tritium (³H), indium (¹¹²In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

5

10

15

20

25

30

35

Further suitable labels for the *Streptococcus* polypeptide-specific antibodies of the present invention are provided below. Examples of suitable enzyme labels include malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast-alcohol dehydrogenase, alpha-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

Examples of suitable radioisotopic labels include ³H, ¹¹¹In, ¹²⁵I, ¹³¹I, ³²P, ³⁵S, ¹⁴C, ⁵¹Cr, ⁵⁷To, ⁵⁸Co, ⁵⁹Fe, ⁷⁵Se, ¹⁵²Eu, ⁹⁰Y, ⁶⁷Cu, ²¹⁷Ci, ²¹¹At, ²¹²Pb, ⁴⁷Sc. ¹⁰⁹Pd. etc. ¹¹¹In is a preferred isotope where *in vivo* imaging is used since its avoids the problem of dehalogenation of the ¹²⁵I or ¹³¹I-labeled monoclonal antibody by the liver. In addition, this radionucleotide has a more favorable gamma emission energy for imaging (Perkins et al., Eur. J. Nucl. Med. 10:296-301 (1985); Carasquillo et al., J. Nucl. Med. 28:281-287 (1987)). For III In example, coupled monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA has shown little uptake in non-tumorous tissues, particularly the liver, and therefore enhances specificity of tumor localization (Esteban et al., J. Nucl. Med. 28:861-870 (1987)).

Examples of suitable non-radioactive isotopic labels include ¹⁵⁷Gd, ⁵⁵Mn, ¹⁶²Dy, ⁵²Tr, and ⁵⁶Fe.

Examples of suitable fluorescent labels include an ¹⁵²Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycocyanin label, an allophycocyanin label, an o-phthaldehyde label, and a fluorescamine label.

Examples of suitable toxin labels include diphtheria toxin, ricin, and cholera toxin.

35

Examples of chemiluminescent labels include a luminal label, an isoluminal label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label.

Examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

5

10

15

20

25

30

35

Typical techniques for binding the above-described labels to antibodies are provided by Kennedy et al., Clin. Chim. Acta 70:1-31 (1976), and Schurs et al., Clin. Chim. Acta 81:1-40 (1977). Coupling techniques mentioned in the latter are the glutaraldehyde method, the periodate method, the dimaleimide method, the m-maleimidobenzyl-N-hydroxy-succinimide ester method, all of which methods are incorporated by reference herein.

In a related aspect, the invention includes a diagnostic kit for use in screening serum containing antibodies specific against *S. pneumoniae* infection. Such a kit may include an isolated *S. pneumoniae* antigen comprising an epitope which is specifically immunoreactive with at least one anti-*S. pneumoniae* antibody. Such a kit also includes means for detecting the binding of said antibody to the antigen. In specific embodiments, the kit may include a recombinantly produced or chemically synthesized peptide or polypeptide antigen. The peptide or polypeptide antigen may be attached to a solid support.

In a more specific embodiment, the detecting means of the above-described kit includes a solid support to which said peptide or polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labelled anti-human antibody. In this embodiment, binding of the antibody to the *S. pneumoniae* antigen can be detected by binding of the reporter labelled antibody to the anti-*S. pneumoniae* antibody.

In a related aspect, the invention includes a method of detecting S. pneumoniae infection in a subject. This detection method includes reacting a body fluid, preferrably serum, from the subject with an isolated S. pneumoniae antigen, and examining the antigen for the presence of bound antibody. In a specific embodiment, the method includes a polypeptide antigen attached to a solid support, and serum is reacted with the support. Subsequently, the support is reacted with a reporter-labelled anti-human antibody. The support is then examined for the presence of reporter-labelled antibody.

The solid surface reagent employed in the above assays and kits is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plates or filter material. These attachment methods generally include non-specific adsorption of the

36

protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

5

10

15

20

25

30

35

Therapeutics and Modes of Administration

The present invention also provides vaccines comprising one or more polypeptides of the present invention. Heterogeneity in the composition of a vaccine may be provided by combining *S. pneumoniae* polypeptides of the present invention. Multi-component vaccines of this type are desirable because they are likely to be more effective in eliciting protective immune responses against multiple species and strains of the *Streptococcus* genus than single polypeptide vaccines. Thus, as discussed in detail below, a multi-component vaccine of the present invention may contain one or more, preferably 2 to about 20, more preferably 2 to about 15, and most preferably 3 to about 8, of the *S. pneumoniae* polypeptides identified in Table 1, or fragments thereof.

Multi-component vaccines are known in the art to elicit antibody production to numerous immunogenic components. Decker, M. and Edwards, K., J. Infect. Dis. 174:S270-275 (1996). In addition, a hepatitis B, diphtheria, tetanus, pertussis tetravalent vaccine has recently been demonstrated to elicit protective levels of antibodies in human infants against all four pathogenic agents. Aristegui, J. et al., Vaccine 15:7-9 (1997).

These vaccines comprise more than one polypeptide, immunogen or antigen. An example of such a multi-component vaccine would be a vaccine comprising more than one of the *S. pneumoniae* polypeptides described in Table 1. A second example is a vaccine comprising one or more, for example 2 to 10, of the *S. pneumoniae* polypeptides identified in Table 1 and one or more, for example 2 to 10, additional polypeptides of either streptococcal or non-streptococcal origin. Thus, a multi-component vaccine which confers protective immunity to both a Streptococcal infection and infection by another pathogenic agent is also within the scope of the invention.

As indicated above, the vaccines of the present invention are expected to elicit a protective immune response against infections caused by species and strains of *Streptococcus* other than strain of *S. pneumoniae* deposited with that ATCC.

Further within the scope of the invention are whole cell and whole viral vaccines. Such vaccines may be produced recombinantly and involve the

expression of one or more of the *S. pneumoniae* polypeptides described in Table 1. For example, the *S. pneumoniae* polypeptides of the present invention may be either secreted or localized intracellular, on the cell surface, or in the periplasmic space. Further, when a recombinant virus is used, the *S. pneumoniae* polypeptides of the present invention may, for example, be localized in the viral envelope, on the surface of the capsid, or internally within the capsid. Whole cells vaccines which employ cells expressing heterologous proteins are known in the art. *See*, *e.g.*, Robinson, K. *et al.*, *Nature Biotech.* 15:653-657 (1997); Sirard, J. *et al.*, *Infect. Immun.* 65:2029-2033 (1997); Chabalgoity, J. *et al.*, *Infect. Immun.* 65:2402-2412 (1997). These cells may be administered live or may be killed prior to administration. Chabalgoity, J. *et al.*, *supra*, for example, report the successful use in mice of a live attenuated *Salmonella* vaccine strain which expresses a portion of a platyhelminth fatty acid-binding protein as a fusion protein on its cells surface.

A multi-component vaccine can also be prepared using techniques known in the art by combining one or more *S. pneumoniae* polypeptides of the present invention, or fragments thereof, with additional non-streptococcal components (e.g., diphtheria toxin or tetanus toxin, and/or other compounds known to elicit an immune response). Such vaccines are useful for eliciting protective immune responses to both members of the *Streptococcus* genus and non-streptococcal pathogenic agents.

The vaccines of the present invention also include DNA vaccines. DNA vaccines are currently being developed for a number of infectious diseases. Boyer, J et al., Nat. Med. 3:526-532 (1997); reviewed in Spier, R., Vaccine 14:1285-1288 (1996). Such DNA vaccines contain a nucleotide sequence encoding one or more S. pneumoniae polypeptides of the present invention oriented in a manner that allows for expression of the subject polypeptide. The direct administration of plasmid DNA encoding B. burgdorgeri OspA has been shown to elicit protective immunity in mice against borrelial challenge. Luke, C. et al., J. Infect. Dis. 175:91-97 (1997).

The present invention also relates to the administration of a vaccine which is co-administered with a molecule capable of modulating immune responses. Kim, J. et al., Nature Biotech. 15:641-646 (1997), for example, report the enhancement of immune responses produced by DNA immunizations when DNA sequences encoding molecules which stimulate the immune response are co-administered. In a similar fashion, the vaccines of the present invention may be co-administered with either nucleic acids encoding immune modulators or the immune modulators. These immune modulators

include granulocyte macrophage colony stimulating factor (GM-CSF) and CD86.

The vaccines of the present invention may be used to confer resistance to streptococcal infection by either passive or active immunization. When the vaccines of the present invention are used to confer resistance to streptococcal infection through active immunization, a vaccine of the present invention is administered to an animal to elicit a protective immune response which either prevents or attenuates a streptococcal infection. When the vaccines of the present invention are used to confer resistance to streptococcal infection through passive immunization, the vaccine is provided to a host animal (e.g., human, dog, or mouse), and the antisera elicited by this antisera is recovered and directly provided to a recipient suspected of having an infection caused by a member of the Streptococcus genus.

5

10

15

20

25

30

35

The ability to label antibodies, or fragments of antibodies, with toxin molecules provides an additional method for treating streptococcal infections when passive immunization is conducted. In this embodiment, antibodies, or fragments of antibodies, capable of recognizing the *S. pneumoniae* polypeptides disclosed herein, or fragments thereof, as well as other *Streptococcus* proteins, are labeled with toxin molecules prior to their administration to the patient. When such toxin derivatized antibodies bind to *Streptococcus* cells, toxin moieties will be localized to these cells and will cause their death.

The present invention thus concerns and provides a means for preventing or attenuating a streptococcal infection resulting from organisms which have antigens that are recognized and bound by antisera produced in response to the polypeptides of the present invention. As used herein, a vaccine is said to prevent or attenuate a disease if its administration to an animal results either in the total or partial attenuation (i.e., suppression) of a symptom or condition of the disease, or in the total or partial immunity of the animal to the disease.

The administration of the vaccine (or the antisera which it elicits) may be for either a "prophylactic" or "therapeutic" purpose. When provided prophylactically, the compound(s) are provided in advance of any symptoms of streptococcal infection. The prophylactic administration of the compound(s) serves to prevent or attenuate any subsequent infection. When provided therapeutically, the compound(s) is provided upon or after the detection of symptoms which indicate that an animal may be infected with a member of the *Streptococcus* genus. The therapeutic administration of the compound(s) serves to attenuate any actual infection. Thus, the *S. pneumoniae* polypeptides, and

39

fragments thereof, of the present invention may be provided either prior to the onset of infection (so as to prevent or attenuate an anticipated infection) or after the initiation of an actual infection.

5

10

15

20

25

30

35

The polypeptides of the invention, whether encoding a portion of a native protein or a functional derivative thereof, may be administered in pure form or may be coupled to a macromolecular carrier. Example of such carriers are proteins and carbohydrates. Suitable proteins which may act as macromolecular carrier for enhancing the immunogenicity of the polypeptides of the present invention include keyhole limpet hemacyanin (KLH) tetanus toxoid, pertussis toxin, bovine serum albumin, and ovalbumin. Methods for coupling the polypeptides of the present invention to such macromolecular carriers are disclosed in Harlow et al., Antibodies: A Laboratory Manual, 2nd Ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1988), the entire disclosure of which is incorporated by reference herein.

A composition is said to be "pharmacologically acceptable" if its administration can be tolerated by a recipient animal and is otherwise suitable for administration to that animal. Such an agent is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient.

While in all instances the vaccine of the present invention is administered as a pharmacologically acceptable compound, one skilled in the art would recognize that the composition of a pharmacologically acceptable compound varies with the animal to which it is administered. For example, a vaccine intended for human use will generally not be co-administered with Freund's adjuvant. Further, the level of purity of the *S. pneumoniae* polypeptides of the present invention will normally be higher when administered to a human than when administered to a non-human animal.

As would be understood by one of ordinary skill in the art, when the vaccine of the present invention is provided to an animal, it may be in a composition which may contain salts, buffers, adjuvants, or other substances which are desirable for improving the efficacy of the composition. Adjuvants are substances that can be used to specifically augment a specific immune response. These substances generally perform two functions: (1) they protect the antigen(s) from being rapidly catabolized after administration and (2) they nonspecifically stimulate immune responses.

Normally, the adjuvant and the composition are mixed prior to presentation to the immune system, or presented separately, but into the same

40

site of the animal being immunized. Adjuvants can be loosely divided into several groups based upon their composition. These groups include oil adjuvants (for example, Freund's complete and incomplete), mineral salts (for example, AlK(SO₄)₂, AlNa(SO₄)₂, AlNH₄(SO₄), silica, kaolin, and carbon), polynucleotides (for example, poly IC and poly AU acids), and certain natural substances (for example, wax D from *Mycobacterium tuberculosis*, as well as substances found in *Corynebacterium parvum*, or *Bordetella pertussis*, and members of the genus *Brucella*. Other substances useful as adjuvants are the saponins such as, for example, Quil A. (Superfos A/S, Denmark). Preferred adjuvants for use in the present invention include aluminum salts, such as AlK(SO₄)₂, AlNa(SO₄)₂, and AlNH₄(SO₄). Examples of materials suitable for use in vaccine compositions are provided in *Remington's Pharmaceutical Sciences* (Osol, A, Ed, Mack Publishing Co, Easton, PA, pp. 1324-1341 (1980), which reference is incorporated herein by reference).

5

10

15

20

25

30

35

The therapeutic compositions of the present invention can be administered parenterally by injection, rapid infusion, nasopharyngeal The absorption (intranasopharangeally), dermoabsorption, orally. administered intramuscularly, may alternatively be compositions Compositions for parenteral administration include sterile intravenously. aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Carriers or occlusive dressings can be used to increase skin permeability and enhance antigen absorption. Liquid dosage forms for oral administration may generally comprise a liposome solution containing the liquid dosage form. Suitable forms for suspending liposomes include emulsions, suspensions, solutions, syrups, and elixirs containing inert diluents commonly used in the art, such as purified water. Besides the inert diluents, such compositions can also include adjuvants, wetting agents, emulsifying and suspending agents, or sweetening, flavoring, or perfuming agents.

Therapeutic compositions of the present invention can also be administered in encapsulated form. For example, intranasal immunization of mice against *Bordetella pertussis* infection using vaccines encapsulated in biodegradable microsphere composed of poly(DL-lactide-co-glycolide) has been shown to stimulate protective immune responses. Shahin, R. et al., Infect. Immun. 63:1195-1200 (1995). Similarly, orally administered encapsulated Salmonella typhimurium antigens have also been shown to elicit protective

41

immunity in mice. Allaoui-Attarki, K. et al., Infect. Immun. 65:853-857 (1997). Encapsulated vaccines of the present invention can be administered by a variety of routes including those involving contacting the vaccine with mucous membranes (e.g., intranasally, intracolonicly, intraduodenally).

5

Many different techniques exist for the timing of the immunizations when a multiple administration regimen is utilized. It is possible to use the compositions of the invention more than once to increase the levels and diversities of expression of the immunoglobulin repertoire expressed by the immunized animal. Typically, if multiple immunizations are given, they will be given one to two months apart.

10

According to the present invention, an "effective amount" of a therapeutic composition is one which is sufficient to achieve a desired biological effect. Generally, the dosage needed to provide an effective amount of the composition will vary depending upon such factors as the animal's or human's age, condition, sex, and extent of disease, if any, and other variables which can be adjusted by one of ordinary skill in the art.

15

The antigenic preparations of the invention can be administered by either single or multiple dosages of an effective amount. Effective amounts of the compositions of the invention can vary from $0.01-1,000~\mu g/ml$ per dose, more preferably $0.1-500~\mu g/ml$ per dose, and most preferably $10-300~\mu g/ml$ per dose.

20

Having now generally described the invention, the same will be more readily understood through reference to the following example which is provided by way of illustration, and is not intended to be limiting of the present invention, unless specified.

25

Examples

Example 1: Expression and Purification of S. pneumoniae Polypeptides in E. coli

30

The bacterial expression vector pQE10 (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311) is used in this example for cloning of the nucleotide sequences shown in Table 1 and for expressing the polypeptides identified in Table 1. The components of the pQE10 plasmid are arranged such that the inserted DNA sequence encoding a polypeptide of the present invention expresses the polypeptide with the six His residues (i.e., a "6 X His tag")) covalently linked to the amino terminus.

35 ·

The DNA sequences encoding the desired portions of the polypeptides of Table 1 are amplified using PCR oligonucleotide primers from either a DNA

library constructed from *S. pnuemonicae*, such as the one deposited by the inventors at the ATCC for convenience, ATCC Deposit No. 97755, or from DNA isolated from the same organism such as the S. pneumoniae strain deposited with the ATCC as Deposit No. 55840. A list of PCR primers which can be used for this purpose is provided in Table 3, below. The PCR primers anneal to the nucleotide sequences encoding both the amino terminal and carboxy terminal amino acid sequences of the desired portion of the polypeptides of Table 1. Additional nucleotides containing restriction sites to facilitate cloning in the pQE10 vector were added to the 5' and 3' primer sequences, respectively. Such restriction sites are listed in Table 3 for each primer. In each case, the primer comprises, from the 5' end, 4 random nucleotides to prevent "breathing" during the annealing process, a restriction site (shown in Table 3), and approximately 15 nucleotides of *S. pneumoniae* ORF sequence (the complete sequence of each cloning primer is shown as SEQ ID NO:227 through SEQ ID NO:452).

5

10

15

20

25 .

30

35

For cloning the polypeptides of Table 1, the 5' and 3' primers were selected to amplify their respective nucleotide coding sequences. One of ordinary skill in the art would appreciate that the point in the protein coding sequence where the 5' primer begins may be varied to amplify a DNA segment encoding any desired portion of the complete amino acid sequences described in Table 1. Similarly, one of ordinary skill in the art would further appreciate that the point in the protein coding sequence where the 3' primer begins may also be varied to amplify a DNA segment encoding any desired portion of the complete amino acid sequences described in Table 1.

The amplified DNA fragment and the pQE10 vector are digested with the appropriate restriction enzyme(s) and the digested DNAs are then ligated together. The ligation mixture is transformed into competent *E. coli* cells using standard procedures such as those described in Sambrook *et al.*, *Molecular Cloning: a Laboratory Manual, 2nd Ed.*; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989). Transformants are identified by their ability to grow under selective pressure on LB plates. Plasmid DNA is isolated from resistant colonies and the identity of the cloned DNA confirmed by restriction analysis, PCR and DNA sequencing.

Clones containing the desired constructs are grown overnight ("O/N") in liquid culture under selection. The O/N culture is used to inoculate a large culture, at a dilution of approximately 1:25 to 1:250. The cells are grown to an optical density at 600 nm ("OD600") of between 0.4 and 0.6. Isopropyl-b-D-thiogalactopyranoside ("IPTG") is then added to a final concentration of 1 mM

43

to induce transcription from the *lac* repressor sensitive promoter, by inactivating the *lac*I repressor. Cells subsequently are incubated further for 3 to 4 hours. Cells are then harvested by centrifugation.

5

1Ò

15

20

25

30

35

The cells are stirred for 3-4 hours at 4 C in 6M guanidine-HCl, pH 8. The cell debris is removed by centrifugation, and the supernatant containing the protein of interest is loaded onto a nickel-nitrilo-tri-acetic acid ("NiNTA") affinity resin column (available from QIAGEN, Inc., supra). Proteins with a 6x His tag bind to the NI-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist, 1995, QIAGEN, Inc., supra). Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH8, then washed with 10 volumes of 6 M guanidine-HCl pH6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.0.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins can be eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

The DNA sequences encoding the amino acid sequences of Table 1 may also be cloned and expressed as fusion proteins by a protocol similar to that described directly above, wherein the pET-32b(+) vector (Novagen, 601 Science Drive, Madison, WI 53711) is preferentially used in place of pQE10.

Each of the polynucleotides shown in Table 1, was successfully amplified and subcloned into pQE10 as described above using the PCR primers shown in Table 3. These pQE10 plasmids containing the DNAs of Table 1, except SP023, SP042, SP054, SP063, SP081, SP092, SP114, SP122, SP123, SP126, and SP127, were deposited with the ATCC as a pooled deposit as a convenience to those of skill in the art. This pooled deposit was desposited on October 16, 1997 and given ATCC Deposit No. 209369. Those of ordinary skill in the art appreciate that isolating an individual plasmid from the pooled deposit is trivial provided the information and reagents described herein. Each of the deposited clones is capable of expressing its encoded *S. pneumoniae* polypeptide.

PCT/US97/19422

5

10

15

20

25

30

44

Example 2: Immunization and Detection of Immune Responses

Methods

Growth of bacterial innoculum, immunization of Mice and Challenge with S pneumoniae.

Propagation and storage of, and challenge by *S. pneumoniae* are preformed essentially as described in Aaberge, I.S. et al., Virulence of *Streptococcus pneumoniae* in mice: a standardized method for preparation and frozen storage of the experimental bacterial inoculum, *Microbial Pathogenesis*, 18:141 (1995), incorporated herein by reference.

Briefly, Todd Hewitt (TH) broth (Difco laboratories, Detroit, MI) with 17% FCS, and horse blood agar plates are used for culturing the bacteria. Both broth and blood plates are incubated at 37°C in a 5% CO₂ atmosphere. Blood plates are incubated for 18 hr. The culture broth is regularly 10-fold serially diluted in TH broth kept at room temperature and bacterial suspensions are kept at room temperature until challenge of mice.

For active immunizations C3H/HeJ mice (The Jackson Laboratory, Bar Harbor, ME) are injected intraperitoneally (i.p.) at week 0 with 20 g of recombinant streptococcal protein, or phosphate-buffered saline (PBS), emulsified with complete Freund's adjuvant (CFA), given a similar booster immunization in incomplete Freund's adjuvant (IFA) at week 4, and challenged at week 6. For challenge *S. pneumoniae* are diluted in TH broth from exponentially-growing cultures and mice are injected subcutaneously (s.c.) at the base of the tail with 0.1 ml of these dilutions (serial dilutions are used to find medium infectious dose). Streptococci used for challenge are passaged fewer than six times *in vitro*. To assess infection, blood samples are obtained from the distal part of the lateral femoral vein into heparinized capillary tubes. A 25 ul blood sample is serially 10-fold diluted in TH broth, and 25 ul of diluted and undiluted blood is plated onto blood agar plates. The plates are incubated for 18 hr. and colonies are counted.

Other methods are known in the art, for example, see Langermann, S. et al., J. Exp. Med., 180:2277 (1994), incorporated herein by reference.

45

Immunoassays

5

10

15

20

25

30

35

Several immunoassay formats are used to quantify levels of streptococcal-specific antibodies (ELISA and immunoblot), and to evaluate the functional properties of these antibodies (growth inhibition assay). The ELISA and immunoblot assays are also used to detect and quantify antibodies elicited in response to streptococcal infection that react with specific streptococcal antigens. Where antibodies to certain streptococcal antigens are elicited by infection this is taken as evidence that the streptococcal proteins in question are expressed *in vivo*. Absence of infection-derived antibodies (seroconversion) following streptococcal challenge is evidence that infection is prevented or suppressed. The immunoblot assay is also used to ascertain whether antibodies raised against recombinant streptococcal antigens recognize a protein of similar size in extracts of whole streptococci. Where the natural protein is of similar, or identical, size in the immunoblot assay to the recombinant version of the same protein, this is taken as evidence that the recombinant protein is the product of a full-length clone of the respective gene.

Enzyme-Linked Immunosorbant Assay (ELISA).

The ELISA is used to quantify levels of antibodies reactive with streptococcus antigens elicited in response to immunization with these streptococcal antigens. Wells of 96 well microtiter plates (Immunlon 4, Dynatech, Chantilly, Virginia, or equivalent) are coated with antigen by incubating 50 l of l g/ml protein antigen solution in a suitable buffer, typically 0.1 M sodium carbonate buffer at pH 9.6. After decanting unbound antigen, additional binding sites are blocked by incubating 100 l of 3% nonfat milk in wash buffer (PBS, 0.2% Tween 20, pH 7.4). After washing, duplicate serial two-fold dilutions of sera in PBS, Tween 20, 1% fetal bovine serum, are incubated for 1 hr, removed, wells are washed three times, and incubated with horseradish peroxidase-conjugated goat anti-mouse IgG. After three washes, bound antibodies are detected with H₂O₂ and 2,2'-azino-di-(3-ethylbenzthiazoline sulfonate) (Schwan, T.G., et al., Proc. Natl. Acad. Sci. USA 92:2909-2913 (1985)) (ABTS®, Kirkegaard & Perry Labs., Gaithersburg, MD) and A₄₀₅ is quantified with a Molecular Devices, Corp. (Menlo Park, California) VmaxTM plate reader. IgG levels background level in serum from naive mice are assigned the minimum titer of 1:100.

46

Sodiumdodecylsulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and Immunoblotting

5

10

15

20

25

30

Using a single well format, total streptococcal protein extracts or recombinant streptococcal antigen are boiled in SDS/2-ME sample buffer before electrophoresis through 3% acrylamide stacking gels, and resolving gels of higher acrylamide concentration, typically 10-15% acrylamide monomer. Gels are electro-blotted to nitrocellulose membranes and lanes are probed with dilutions of antibody to be tested for reactivity with specific streptococcal antigens, followed by the appropriate secondary antibody-enzyme (horseradish peroxidase) conjugate. When it is desirable to confirm that the protein had transferred following electro-blotting, membranes are stained with Ponceau S. Immunoblot signals from bound antibodies are detected on x-ray film as chemiluminescence using ECLTM reagents (Amersham Corp., Arlington Heights, Illinois).

Example 3: Detection of Streptococcus mRNA expression

Northern blot analysis is carried out using methods described by, among others, Sambrook *et al.*, *supra*. to detect the expression of the *S. pneumoniae* nucleotide sequences of the present invention in animal tissues. A cDNA probe containing an entire nucleotide sequence shown in Table 1 is labeled with ³²P using the *redi*primeTM DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using a CHROMA SPIN-100TM column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to detect the expression of *Streptococcus* mRNA in an animal tissue sample.

Animal tissues, such as blood or spinal fluid, are examined with the labeled probe using ExpressHybTM hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 C overnight, and films developed according to standard procedures.

47

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

5

The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

WO 98/18930

48

SP001 nucleotide (SEQ ID NO:1)

TAAAATCTACGACAATAAAAATCAACTCATTGCTGACTTGGGTTCTGAACGCCGCGTCAATGCCCAAGC TAATGATATTCCCACAGATTTGGTTAAGGCAATCGTTTCTATCGAAGACCATCGCTTCTTCGACCACAG GGGGATTGATACCATCCGTATCCTGGGAGCTTTCTTGCGCAATCTGCAAAGCAATTCCCTCCAAGGTGG ATCAACTCTCACCCAACAGTTGATTAAGTTGACTTACTTTTCAACTTCGACTTCCGACCAGACTATTTC CTACTATATAAATAAGGTCTACATGTCTAATGGGAACTATGGAATGCAGACAGCAGCTCAAAACTACTA CCAATATGACCCCTATTCACATCCAGAAGCAGCCCAAGACCGCCGAAACTTGGTCTTATCTGAAATGAA AAATCAAGGCTACATCTCTGCTGAACAGTATGAGAAAGCAGTCAATACACCAATTACTGATGGACTACA TCAAAAACATCTGTGGGATATTTACAATACAGACGAATACGTTGCCTATCCAGACGATGAATTGCAAGT CGCTTCTACCATTGTTGATGTTTCTAACGGTAAAGTCATTGCCCAGCTAGGAGCACGCCATCAGTCAAG CACAGACTATGCTCCTGCCTTGGAGTACGGTGTCTACGATTCAACTGCTACTATCGTTCACGATGAGCC CTATAACTACCCTGGGACAAATACTCCTGTTTATAACTGGGATAGGGGCTACTTTGGCAACATCACCTT GCAATACGCCCTGCAACAATCGCGAAACGTCCCAGCCGTGGAAACTCTAAACAAGGTCGGACTCAACCG CGCCAAGACTTTCCTAAATGGTCTAGGAATCGACTACCCAAGTATTCACTACTCAAATGCCATTTCAAG TAACACAACCGAATCAGACAAAAAATATGGAGCAAGTAGTGAAAAGATGGCTGCTGCTTACGCTGCCTT TGCAAATGGTGGAACTTACTATAAACCAATGTATATCCATAAAGTCGTCTTTAGTGATGGGAGTGAAAA AGAGTTCTCTAATGTCGGAACTCGTGCCATGAAGGAAACGACAGCCTATATGATGACCGACATGATGAA AACCTCTAACTATACAGACGAGGAAATTGAAAACCACATCAAGACCTCTCAATTTGTAGCACCTGATGA ACTATTTGCTGGCTATACGCGTAAATATTCAATGGCTGTATGGACAGGCTATTCTAACCGTCTGACACC AAGCAATCCAGAAGATTGGAATATACCAGAGGGGCTCTACAGAAATGGAGAATTCGTATTTAAAAATGG TGCTCGTTCTACGTGGAACTCACCTGCTCCACAACAACCCCCATCAACTGAAAGTTCAAGCTCATCATC AGATAGTTCAACTTCACAGTCTAGCTCAACCACTCCAAGCACAAATAATAGTACGACTACCAATCCTAA CAATAATACGCAACAATCAAATACAACCCCTGATCAACAAAATCAGAATCCTCAACCAGCACAACCA

SP001 AMINO ACID (SEQ ID NO:2)

KIYDNKNQLIADLGSERRVNAQANDIPTDLVKAIVSIEDHRFFDHRGIDTIRILGAFLRNLQSNSLQGG STLTQQLIKLTYFSTSTSDQTISRKAQEAWLAIQLEQKATKQEILTYYINKVYMSNGNYGMQTAAQNYY GKDLNNLSLPQLALLAGMPQAPNQYDPYSHPEAAQDRRNLVLSEMKNQGYISAEQYEKAVNTPITDGLQ SLKSASNYPAYMDNYLKEVINQVEEETGYNLLTTGMDVYTNVDQEAQKHLWDIYNTDEYVAYPDDELQV ASTIVDVSNGKVIAQLGARHQSSNVSFGINQAVETNRDWGSTMKPITDYAPALEYGVYDSTATIVHDEP YNYPGTNTPVYNWDRGYFGNITLQYALQQSRNVPAVETLNKVGLNRAKTFLNGLGIDYPSIHYSNAISS NTTESDKKYGASSEKMAAAYAAFANGGTYYKPMYIHKVVFSDGSEKEFSNVGTRAMKETTAYMMTDMMK TVLTYGTGRNAYLAWLPQAGKTGTSNYTDEEIENHIKTSQFVAPDELFAGYTRKYSMAVWTGYSNRLTPLVGNGLTVAAKVYRSMMTYLSEGSNPEDWNIPEGLYRNGEFVFKNGARSTWNSPAPQQPPSTESSSSSS DSSTSQSSSTTPSTNNSTTTNPNNNTQQSNTTPDQQNQNPQPAQP

SP004 nucleotide (SEQ ID NO:3)

49

SP004 amino acid (SEQ ID NO:4)

NYNTDYELTSGEKLPLPKEISGYTYIGYIKEGKTTSESEVSNQKSSVATPTKQQKVDYNVTPNFVDHPS
TVQAIQEQTPVSSTKPTEVQVVEKPFSTELINPRKEEKQSSDSQEQLAEHKNLETKKEEKISPKEKTGV
NTLNPQDEVLSGQLNKPELLYREETMETKIDFQEEIQENPDLAEGTVRVKQEGKLGKKVEIVRIFSVNK
EEVSREIVSTSTTAPSPRIVEKGTKKTQVIKEQPETGVEHKDVQSGAIVEPAIQPELPEAVVSDKGEPE
VQPTLPEAVVTDKGETEVQPESPDTVVSDKGEPEQVAPLPEYKGNIEQVKPETPVEKTKEQGPEKTEEV
PVKPTEETPVNPNEGTTEGTSIQEAENPVQPAEESTTNSEKVSPDTSSKNTGEVSSNPSDSTTSVGESN
KPEHNDSKNENSEKTVEEVPVNPNEGTVEGTSNQETEKPVQPAEETQTNSGKIANENTGEVSNKPSDSK
PPVEESNQPEKNGTATKPENSGNTTSENGQTEPEPSNGNSTEDVSTESNTSNSNGNEEIKQENELDPDK
KVEEPEKTLELRNVSDLEL

SP006 nucleotide (SEQ ID NO:5)

TGAGAATCAAGCTACACCCAAAGAGACTAGCGCTCAAAAGACAATCGTCCTTGCTACAGCTGGCGACGT
GCCACCATTTGACTACGAAGACAAGGGCAATCTGACAGGCTTTGATATCGAAGTTTTAAAGGCAGTAGA
TGAAAAACTCAGCGACTACGAGATTCAATTCCAAAGAACCGCCTGGGAGAGCATCTTCCCAGGACTTGA
TTCTGGTCACTATCAGGCTGCGGCCAATAACTTGAGTTACACAAAAAGAGCGTGCTGAAAAATACCTTTA
CTCGCTTCCAATTTCCAACAATCCCCTCGTCCTTGTCAGCAACAAGAAAAATCCTTTGACTTCTCTTGA
CCAGATCGCTGGTAAAACAACACAAGAGGATACCGGAACTTCTAACGCTCAATTCATCAATAACTGGAA
TCAGAAACACACTGATAATCCCGCTACAATTAATTTTTCTGGTGAGGATATTGGTAAACGAATCCTAGA
CCTTGCTAACGGAGAGTTTGATTTCCTAGTTTTTTGACAAGGTTCCAAAAAAGATTATATCATTTTCTCAAG
CGGTTTAGACCTCTCAGTCGTTGATTTACCTTCTGCAGATAGCCCCAGCAATTATATCATTTTCTCAAG
CGACCAAAAAAGAGTTTAAAGAGCAATTTGATAAAGCGCTCAAAGAACTCTATCAAGACCGTTGA
AAAACTCAGCAATACCTATCTAGGTGGTTCTTACCTCCCAGATCAATCTCAGTTACAA

SP006 amino acid (SEQ ID NO:6)

ENQATPKETSAQKTIVLATAGDVPPFDYEDKGNLTGFDIEVLKAVDEKLSDYEIQFQRTAWESIFPGLD SGHYQAAANNLSYTKERAEKYLYSLPISNNPLVLVSNKKNPLTSLDQIAGKTTQEDTGTSNAQFINNWN QKHTDNPATINFSGEDIGKRILDLANGEFDFLVFDKVSVQKIIKDRGLDLSVVDLPSADSPSNYIIFSS DOKEFKEOFDKALKELYQDGTLEKLSNTYLGGSYLPDQSQLQ

SP007 nucleotide (SEQ ID NO:7)

SP007 amino acid (SEQ ID NO:8)

GNRSSRNAASSSDVKTKAAIVTDTGGVDDKSFNQSAWEGLQAWGKEHNLSKDNGFTYFQSTSEADYANN LQQAAGSYNLIFGVGFALNNAVKDAAKEHTDLNYVLIDDVIKDQKNVASVTFADNESGYLAGVAAAKTT KTKQVGFVGGIESEVISRFEAGFKAGVASVDPSIKVQVDYAGSFGDAAKGKTIAAAQYAAGADIVYQVA GGTGAGVFAEAKSLNESRPENEKVWVIGVDRDQEAEGKYTSKDGKESNFVLVSTLKQVGTTVKDISNKA ERGEFPGGQVIVYSLKDKGVDLAVTNLSEEGKKAVEDAKAKILDGSVKVPEK

SP008 nucleotide (SEQ ID NO:9)

TGTGGAAATTTGACAGGTAACAGCAAAAAAGCTGCTGATTCAGGTGACAAACCTGTTATCAAAATGTAC CAAATCGGTGACAAACCAGACAACTTGGATGAATTGTTAGCAAATGCCAACAAAATCATTGAAGAAAAA GTTGGTGCCAAATTGGATATCCAATACCTTGGCTGGGGTGACTATGGTAAGAAAATGTCAGTTATCACA TCATCTGGTGAAAACTATGATATTGCCTTTGCAGATAACTATATTGTAAATGCTCAAAAAGGTGCTTAC GCTGACTTGACAGAATTGTACAAAAAAGAAGGTAAAGACCTTTACAAAGCACTTGACCCAGCTTACATC AAGGGTAATACTGTAAATGGTAAGATTTACGCTGTTCCAGTTGCAGCCAACGTTGCATCATCTCAAAAC TTTGCCTTCAACGGAACTCTCCTTGCTAAATATGGTATCGATATTTCAGGTGTTACTTCTTACGAAACT CTTGAGCCAGTCTTGAAACAAATCAAAGAAAAAGCTCCAGACGTAGTACCATTTGCTATTGGTAAAGTT TTCATCCCATCTGATAATTTTGACTACCCAGTAGCAAACGGTCTTCCATTCGTTATCGACCTTGAAGGC GATACTACTAAAGTTGTAAACCGTTACGAAGTGCCTCGTTTCAAAGAACACTTGAAGACTCTTCACAAA TTCTATGAAGCTGGCTACATTCCAAAAGACGTCGCAACAAGCGATACTTCCTTTGACCTTCAACAAGAT AACAAAGATATCCAAATCAAACCAATTACTAACTTCATCAAGNAAAACCAAACAACAACAAGTTGCTAAC TTTGTCATCTCAAACAACTCTAAGAACAAAGAAAAATCAATGGAAATCTTGAACCTCTTGAATACGAAC CCAGAACTCTTGAACGGTCTTGTTTACGGTCCAGAAGGCAAGAACTGGGAAAAAATTGAAGGTAAAGAA GCTAAAGAATCTCCAGCGCTTGGATTTATCTTCAATACTGACAATGTGAAAATCTGAAAATCTCAGCTATT GCTAACACAATGCAACAATTTGATACAGCTATCAACACTGGTACTGTAGACCCAGATAAAGCGATTCCA GAATTGATGGAAAAATTGAAATCTGAAGGTGCCTACGAAAAAGTATTGAACGAAATGCAAAAACAATAC GATGAATTCTTGAAAAAACAAAAAA

SP008 amino acid (SEQ ID NO:10)

CGNLTGNSKKAADSGDKPVIKMYQIGDKPDNLDELLANANKIIEEKVGAKLDIQYLGWGDYGKKMSVIT SSGENYDIAFADNYIVNAQKGAYADLTELYKKEGKDLYKALDPAYIKGNTVNGKIYAVPVAANVASSQN FAFNGTLLAKYGIDISGVTSYETLEPVLKQIKEKAPDVVPFAIGKVFIPSDNFDYPVANGLPFVIDLEG DTTKVVNRYEVPRFKEHLKTLHKFYEAGYIPKDVATSDTSFDLQQDTWFVREETVGPADYGNSLLSRVA NKDIQIKPITNFIKXNQTTQVANFVISNNSKNKEKSMEILNLLNTNPELLNGLVYGPEGKNWEKIEGKE NRVRVLDGYKGNTHMGGWNTGNNWILYINENVTDQQIENSKKELAEAKESPALGFIFNTDNVKSEISAI ANTMQQFDTAINTGTVDPDKAIPELMEKLKSEGAYEKVLNEMQKQYDEFLKNKK

SP009 nucleotide (SEQ ID NO:11)

SP009 amino acid (SEQ ID NO:12)

GQGTASKDNKEAELKKVDFILDWTPNTNHTGLYVAKEKGYFKEAGVDVDLKLPPEESSSDLVINGKAPF AVYFQDYMAKKLEKGAGITAVAAIVEHNTSGIISRKSDNVSSPKDLVGKKYGTWNDPTELAMLKTLVES QGGDFEKVEKVPNNDSNSITPIANGVFDTAWIYYGWDGILAKSQGVDANFMYLKDYVKEFDYYSPVIIA NNDYLKDNKEEARKVIQAIKKGYQYAMEHPEEAADILIKNAPELKEKRDFVIESQKYLSKEYASDKEKW GQFDAARWNAFYKWDKENGILKEDLTDKGFTNEFVK

51

SP010 nucleotide (SEQ ID NO:13)

SP010 amino acid (SEQ ID NO:14)

SSGGNAGSSSGKTTAKARTIDEIKKSGELRIAVFGDKKPFGYVDNDGSTKVRYDIELGNQLAQDLGVKV
KYISVDAANRAEYLISNKVDITLANFTVTDERKKQVDFALPYMKVSLGVVSPKTGLITDVKQLEGKTLI
VTKGTTAETYFEKNHPEIKLQKYDQYSDSYQALLDGRGDAFSTDNTEVLAWALENKGFEVGITSLGDPD
TIAAAVQKGNQELLDFINKDIEKLGKENFFHKAYEKTLHPTYGDAAKADDLVVEGGKVD

SP011 nucleotide (SEQ ID NO:15)

CTCCAACTATGGTAAATCTGCGGATGGCACAGTGACCATCGAGTATTTCAACCAGAAAAAAAGAAATGAC CAAAACCTTGGAAGAAATCACTCGTGATTTTGAGAAGGAAAACCCTAAGATCAAGGTCAAAGTCGTCAA TGTACCAAATGCTGGTGAAGTATTGAAGACACGCGTTCTCGCAGGAGATGTGCCTGATGTGGTCAATAT TTACCCACAGTCCATCGAACTGCAAGAATGGGCAAAAGCAGGTGTTTTTGAAGATTTGAGCAACAAAGA CTACCTGAAACGCGTGAAAAATGGCTACGCTGAAAAATATGCTGTAAACGAAAAAGTTTACAACGTTCC TTTTACAGCTAATGCTTATGGAATTTACTACAACAAAGATAAATTCGAAGAACTGGGCTTGAAGGTTCC TGAAACCTGGGATGAATTTGAACAGTTAGTCAAAGATATCGTTGCTAAAGGACAAACACCATTTGGAAT AAAAGAAGCAAATCAATACCTTCGTTATTCTCAACCAAATGCCATTAAATTGTCGGATCCGATTATGAA AGATGATATCAAGGTCATGGACATCCTTCGCATCAATGGATCTAAGCAAAAGAACTGGGAAGGTGCTGG CTATACCGATGTTATCGGAGCCTTCGCACGTGGGGATGTCCTCATGACACCAAATGGGTCTTGGGCGAT CACAGCGATTAATGAACAAAAACCGAACTTTAAGATTGGGACCTTCATGATTCCAGGAAAAGAAAAAGG ACAAAGCTTAACCGTTGGTGCGGGAGACTTGGCATGGTCTATCTCAGCCACCACCAAACATCCAAAAGA AGCCAATGCCTTTGTGGAATATATGACCCGTCCAGAAGTCATGCAAAAATACTACGATGTGGACGGATC TCCAACAGCGATCGAAGGGGTCAAACAAGCAGGAGAAGATTCACCGCTTGCTGGTATGACCGAATATGC CTTTACGGATCGTCACTTGGTCTGGTTGCAACAATACTGGACCAGTGAAGCAGACTTCCATACCTTGAC CATGAACTATGTCTTGACCGGTGATAAACAAGGCATGGTCAATGATTTGAATGCCTTCTTTAACCCGAT GAAAGCGGATGTGGAT

SP011 amino acid (SEQ ID NO:16)

SNYGKSADGTVTIEYFNQKKEMTKTLEEITRDFEKENPKIKVKVVNVPNAGEVLKTRVLAGDVPDVVNI YPQSIELQEWAKAGVFEDLSNKDYLKRVKNGYAEKYAVNEKVYNVPFTANAYGIYYNKDKFEELGLKVP ETWDEFEQLVKDIVAKGQTPFGIAGADAWTLNGYNQLAFATATGGGKEANQYLRYSQPNAIKLSDPIMK DDIKVMDILRINGSKQKNWEGAGYTDVIGAFARGDVLMTPNGSWAITAINEQKPNFKIGTFMIPGKEKG QSLTVGAGDLAWSISATTKHPKEANAFVEYMTRPEVMQKYYDVDGSPTAIEGVKQAGEDSPLAGMTEYA FTDRHLVWLQOYWTSEADFHTLTMNYVLTGDKQGMVNDLNAFFNPMKADVD

SP012 nucleotide (SEQ ID NO:17)

WO 98/18930

Table 1

52

SP012 nucleotide (SEQ ID NO:18)

GKNSSETSGDNWSKYQSNKSITIGFDSTFVPMGFAQKDGSYAGFDIDLATAVFEKYGITVNWQPIDWDL KEAELTKGTIDLIWNGYSATDERREKVAFSNSYMKNEQVLVTKKSSGITTAKDMTGKTLGAQAGSSGYA DFEANPEILKNIVANKEANQYQTFNEALIDLKNDRIDGLLIDRVYANYYLEAEGVLNDYNVFTVGLETE AFAVGARKEDTNLVKKINEAFSSLYKDGKFQEISQKWFGEDVATKEVKEGQ

SP013 nucleotide (SEQ ID NO:19)

SP013 amino acid (SEQ ID NO:20)

ASGKKDTTSGQKLKVVATNSIIADITKNIAGDKIDLHSIVPIGQDPHEYEPLPEDVKKTSEANLIFYNG INLETGGNAWFTKLVENAKKTENKDYFAVSDGVDVIYLEGQNEKGKEDPHAWLNLENGIIFAKNIAKQL SAKDPNNKEFYEKNLKEYTDKLDKLDKESKDKFNKIPAEKKLIVTSEGAFKYFSKAYGVPSAYIWEINT EEEGTPEQIKTLVEKLRQTKVPSLFVESSVDDRPMKTVSQDTNIPIYAQIFTDSIAEQGKEGDSYYSMM KYNLDKIAEGLAK

SP014 nucleotide (SEQ ID NO:21)

TGGCTCAAAAAATACAGCTTCAAGTCCAGATTATAAGTTGGAAGGTGTAACATTCCCGCTTCAAGAAAA GAAAACATTGAAGTTTATGACAGCCAGTTCACĆGTTATCTCCTAAAGACCCAAATGAAAAGTTAATTTT GCAACGTTTGGAGAAGGAAACTGGCGTTCATATTGACTGGACCAACTACCAATCCGACTTTGCAGAAAA ACGTAACTTGGATATTTCTAGTGGTGATTTACCAGATGCTATCCACAACGACGAGCTTCAGATGTGGA TCTTAAGAAAATTTTGGATGAGAAACCAGAGTACAAGGCCTTGATGACAGCACCTGATGGGCACATTTA CTCATTTCCATGGATTGAAGAGCTTGGAGATGGTAAAGAGTCTATTCACAGTGTCAACGATATGGCTTG GATTAACAAAGATTGGCTTAAGAAACTTGGTCTTGAAATGCCAAAAACTACTGATGATTTGATTAAAGT CCTAGAAGCTTTCAAAAACGGGGATCCAAATGGAAATGGAGGGCTGATGAAATTCCATTTTCATTTAT TAGTGGTAACGGAAACGAAGATTTTAAATTCCTATTTGCTGCATTTGGTATAGGGGGATAACGATGATCA TTTAGTAGTAGGAAATGATGGCAAAGTTGACTTCACAGCAGATAACGATAACTATAAAGAAGGTGTCAA ATTTATCCGTCAATTGCAAGAAAAAGGCCTGATTGATAAAGAAGCTTTCGAACATGATTGGAATAGTTA CATTGCTAAAGGTCATGATCAGAAATTTGGTGTTTACTTTACATGGGATAAGAATAATGTTACTGGAAG TAACGAAAGTTATGATGTTTTACCAGTACTTGCTGGACCAAGTGGTCAAAAACACGTAGCTCGTACAAA CGGTATGGGATTTGCACGTGACAAGATGGTTATTACCAGTGTAAACAAAAACCTAGAATTGACAGCTAA ATGGATTGATGCACAATACGCTCCACTCCAATCTGTGCAAAATAACTGGGGAACTTACGGAGATGACAA ACAACAAAACATCTTTGAATTGGATCAAGCGTCAAATAGTCTAAAACACTTACCACTAAAACGGAACTGC ACCAGCAGAACTTCGTCAAAAGACTGAAGTAGGAGGACCACTAGCTATCCTAGATTCATACTATGGTAA AGTAACAACCATGCCTGATGATGCCAAATGGCGTTTGGATCTTATCAAAGAATATTATGTTCCTTACAT

·

GAGCAATGTCAATAACTATCCAAGAGTCTTTATGACACAGGAAGATTTGGACAAGATTGCCCATATCGA AGCAGATATGAATGACTATATCTACCGTAAACGTGCTGAATGGATTGTAAATGGCAATATTGATACTGA GTGGGATGATTACAAGAAAGAACTTGAAAAATACGGACTTTCTGATTACCTCGCTATTAAACAAAAATA CTACGACCAATACCAAGCAAACAAAAAC

53

SP014 amino acid (SEQ ID NO:22)

GSKNTASSPDYKLEGVTFPLQEKKTLKFMTASSPLSPKDPNEKLILQRLEKETGVHIDWTNYQSDFAEK RNLDISSGDLPDAIHNDGASDVDLMNWAKKGVIIPVEDLIDKYMPNLKKILDEKPEYKALMTAPDGHIY SFPWIEELGDGKESIHSVNDMAWINKDWLKKLGLEMPKTTDDLIKVLEAFKNGDPNGNGEADEIPFSFI SGNGNEDFKFLFAAFGIGDNDDHLVVGNDGKVDFTADNDNYKEGVKFIRQLQEKGLIDKEAFEHDWNSY IAKGHDQKFGVYFTWDKNNVTGSNESYDVLPVLAGPSGQKHVARTNGMGFARDKMVITSVNKNLELTAK WIDAQYAPLQSVQNNWGTYGDDKQQNIFELDQASNSLKHLPLNGTAPAELRQKTEVGGPLAILDSYYGK VTTMPDDAKWRLDLIKEYYVPYMSNVNNYPRVFMTQEDLDKIAHIEADMNDYIYRKRAEWIVNGNIDTE WDDYKKELEKYGLSDYLAIKQKYYDQYQANKN

SP015 nucleotide (SEQ ID NO:23)

SP015 amino acid (SEQ ID NO:24)

STNSSTSQTETSSSAPTEVTIKSSLDEVKLSKVPEKIVTFDLGAADTIRALGFEKNIVGMPTKTVPTYL KDLVGTVKNVGSMKEPDLEAIAALEPDLIIASPRTQKFVDKFKEIAPTVLFQASKDDYWTSTKANIESL ASAFGETGTQKAKEELTKLDKSIQEVATKNESSDKKALAILLNEGKMAAFGAKSRFSFLYQTLKFKPTD TKFEDSRHGQEVSFESVKEINPDILFVINRTLAIGGDNSSNDGVLENALIAETPAAKNGKIIQLTPDLW YLSGGGLESTKLMIEDIQKALK

SP016 nucleotide (SEQ ID NO:25)

TGGCAATTCTGGCGGAAGTAAAGATGCTGCCAAATCAGGTGGTGACGGTGCCAAAACAGAAATCACTTG CGAAGCGTTTGAAAAAGCAAACCCAGATATAAAAGTGAAATTGGAAACCATCGACTTCAAGTCAGGTCC TGAAAAAATCACAACAGCCATCGAAGCAGGAACAGCTCCAGACGTACTCTTTGATGCACCAGGACGTAT CATCCAATACGGTAAAAACGGTAAATTGGCTGAGTTGAATGACCTCTTCACAGATGAATTTGTTAAAGA TGTCAACAATGAAAACATCGTACAAGCAAGTAAAGCTGGAGACAAGGCTTATATGTATCCGATTAGTTC TGCCCCATTCTACATGGCAATGAACAAGAAAATGTTAGAAGATGCTGGAGTAGCAAACCTTGTAAAAGA AGGTTGGACAACTGATGATTTTGAAAAAGTATTGAAAGCACTTAAAGACAAGGGTTACACACCAGGTTC ATTGTTCAGTTCTGGTCAAGGGGGAGACCAAGGAACACGTGCCTTTATCTCTAACCTTTATAGCGGTTC TGTAACAGATGAAAAAGTTAGCAAATATACAACTGATGATCCTAAATTCGTCAAAGGTCTTGAAAAAGC AACTAGCTGGATTAAAGACAATTTGATCAATAATGGTTCACAATTTGACGGTGGGGCAGATATCCAAAA CTTTGCCAACGGTCAAACATCTTACACAATCCTTTGGGCACCAGCTCAAAATGGTATCCAAGCTAAACT TTTAGAAGCAAGTAAGGTAGAAGTGGTAGAAGTACCATTCCCATCAGACGAAGGTAAGCCAGCTCTTGA GTACCTTGTAAACGGGTTTGCAGTATTCAACAATAAAGACGACAAGAAAGTCGCTGCATCTAAGAAATT CATCCAGTTTATCGCAGATGACAAGGAGTGGGGACCTAAAGACGTAGTTCGTACAGGTGCTTTCCCAGT CCGTACTTCATTTGGAAAACTTTATGAAGACAAACGCATGGAAACAATCAGCGGCTGGACTCAATACTA CTCACCATACTACAACACTATTGATGGATTTGCTGAAATGAGAACACTTTGGTTCCCAATGTTGCAATC CAAAAAGCTATGAAACAA

Table 1 54

SP016 amino acid (SEQ ID NO:26)

GNSGGSKDAAKSGGDGAKTEITWWAFPVFTQEKTGDGVGTYEKSIIEAFEKANPDIKVKLETIDFKSGP EKITTAIEAGTAPDVLFDAPGRIIQYGKNGKLAELNDLFTDEFVKDVNNENIVQASKAGDKAYMYPISS APFYMAMNKKMLEDAGVANLVKEGWTTDDFEKVLKALKDKGYTPGSLFSSGQGGDQGTRAFISNLYSGS VTDEKVSKYTTDDPKFVKGLEKATSWIKDNLINNGSQFDGGADIQNFANGQTSYTILWAPAQNGIQAKL LEASKVEVVEVPFPSDEGKPALEYLVNGFAVFNNKDDKKVAASKKFIQFIADDKEWGPKDVVRTGAFPV RTSFGKLYEDKRMETISGWTQYYSPYYNTIDGFAEMRTLWFPMLQSVSNGDEKPADALKAFTEKANETI KKAMKO

SP017 nucleotide (SEQ ID NO:27)

SP017 amino acid (SEQ ID NO:28)

SQEKTKNEDGETKTEQTAKADGTVGSKSQGAAQKKAEVVNKGDYYSIQGKYDEIIVANKHYPLSKDYNP GENPTAKAELVKLIKAMQEAGFPISDHYSGFRSYETQTKLYQDYVNQDGKAAADRYSARPGYSEHQTGL AFDVIGTDGDLVTEEKAAQWLLDHAADYGFVVRYLKGKEKETGYMAEEWHLRYVGKEAKEIAASGLSLE EYYGFEGGDYVD

SP019 nucleotide (SEQ ID NO:29)

SP019 amino acid (SEQ ID NO:30)

KGLWSNNLTCGYDEKIILENINIKIPEEKISVIIGSNGCGKSTLIKTLSRLIKPLEGEVLLDNKSINSY KEKDLAKHIAILPQSPIIPESITVADLVSRGRFPYRKPFKSLGKDDLEIINRSMVKANVEDLANNLVEE LSGGQRQRVWIALALAQDTSILLLDEPTTYLDISYQIELLDLLTDLNQKYKTTICMILHDINLTARYAD YLFAIKEGKLVAEGKPEDILNDKLVKDIFNLEAKIIRDPISNSPLMIPIGKHHVS

SP020 nucleotide (SEQ ID NO:31)

TGCTATCAAGAAAGTAATCGCAGCTTACCACACAGATGACGTGAAAAAAGTTATCGAAGAATCATCAGA TGGTTTGGATCAACCAGTTTGG

55

SP020 amino acid (SEQ ID NO:32)

NSEKKADNATTIKIATVNRSGSEEKRWDKIQELVKKDGITLEFTEFTDYSQPNKATADGEVDLNAFQHY NFLNNWNKENGKDLVAIADTYISPIRLYSGLNGSANKYTKVEDIPANGEIAVPNDATNESRALYLLQSA GLIKLDVSGTALATVANIKENPKNLKITELDASQTARSLSSVDAAVVNNTFVTEAKLDYKKSLFKEQAD ENSKQWYNIIVAKKDWETSPKADAIKKVIAAYHTDDVKKVIEESSDGLDQPVW

SP021 nucleotide (SEQ ID NO:33)

SP021 amino acid (SEQ ID NO:34)

SKGSEGADLISMKGDVITEHQFYEQVKSNPSAQQVLLNMTIQKVFEKQYGSELDDKEVDDTIAEEKKQY GENYQRVLSQAGMTLETRKAQIRTSKLVELAVKKVAEAELTDEAYKKAFDEYTPDVTAQIIRLNNEDKA KEVLEKAKAEGADFAQLAKDNSTDEKTKENGGEITFDSASTEVPGASPKKPLFAFRCGMVFLDVDYSNW GTPSLO

SP022 nucleotide (SEQ ID NO:35)

SP022 amino acid (SEQ ID NO:36)

GMAAFKNPNNQYKAITIAQTLGDDASSEELAGRYGSAVQCTEVTASNLSTVKTKATVVEKPLKDFRAST SDQSGWVESNGKWYFYESGDVKTGWVKTDGKWYYLNDLGVMQTGFVKFSGSWYYLSNSGAMFTGWGTDG SRWFYFDGSGAMKTGWYKENGTWYYLDEAGIMKTGWFKVGPHWYYAYGSGALAVSTTTPDGYRVNGNGE WVN

SP023 nucleotide (SEQ ID NO:37)

CTGGAAACAAGAAAACGGTATGTGGTACTTCTACAATACTGATGGTTCAATGGCGACAGGATGGCTCCA AAACAATGGCTCATGGTACTACCTCAACAGCAATGGCGCTATGGCGACAGGATGGCTCCAAAACAATGG TTCATGGTACTATCTAAACGCTAATGGTTCAATGGCAACAGGATGGCTCCAAAACAATGGTTCATGGTA CTACCTAAACGCTAATGGTTCAATGGCGACAGGATGGCTCCAATACAATGGCTCATGGTACTACCTAAA CGCTAATGGTTCAATGGCGACAGGATGGCTCCAATACAATGGCTCATGGTACTACCTAAACGCTAATGG TGATATGGCGACAGGTTGGGTGAAAGATGGAGATACCTGGTACTATCTTGAAGCATCAGGTGCTATGAA AGCAAGCCAATGGTTCAAAGTATCAGATAAATGGTACTATGTCAATGGCTCAGGTGCCCTTGCAGTCAA ${\tt CACAACTGTAGATGGCTATGGAGTCAATGCCAATGGTGAATGGGTAAAC}$

SP023 amino acid (SEQ ID NO:38)

DEOKIKOAEAEVESKOAEATRLKKIKTDREEAEEEAKRRADAKEQGKPKGRAKRGVPGELATPDKKEND AKSSDSSVGEETLPSPSLKPEKKVAEAEKKVEEAKKKAEDQKEEDRRNYPTNTYKTLELEIAESDVEVK KAELELVKEEAKEPRNEEKVKQAKAEVESKKAEATRLEKIKTDRKKAEEEAKRKAAEEDKVKEKPAEQP QPAPAPKAEKPAPAPKPENPAEQPKAEKPADQQAEEDYARRSEEEYNRLTQQQPPKTEKPAQPSTPKTG WKQENGMWYFYNTDGSMATGWLQNNGSWYYLNSNGAMATGWLQNNGSWYYLNANGSMATGWLQNNGSWY YLNANGSMATGWLQYNGSWYYLNANGSMATGWLQYNGSWYYLNANGDMATGWVKDGDTWYYLEASGAMK ASOWFKVSDKWYYVNGSGALAVNTTVDGYGVNANGEWVN

SP025 nucleotide (SEQ ID NO:39)

CTGTGGTGAGGAAGAACTAAAAAGACTCAAGCAGCACAACAGCCAAAACAACAACAACGACTGTACAACA TGATTTTAAGGGTAAAAAGGTTTACTTGAAGTTTTGGGCTTCATGGTGTGGTCCATGCAAGAAAAGTAT ${\tt GCCAGAGTTGATGGAACTAGCGGCGAAACCAGATCGTGATTTCGAAATTCTTACTGTCATTGCACCAGG}$ AATTCAAGGTGAAAAAACTGTTGAGCAATTCCCACAATGGTTCCAGGAACAAGGATATAAGGATATCCC AGTTCTTTATGATACCAAAGCAACCACTTCCAAGCTTATCAAATTCGAAGCATTCCTACAGAATATT

SP025 amino acid (SEQ ID NO:40)

 ${\tt CGEEETKKTQAAQQPKQQTTVQQIAVGKDAPDFTLQSMDGKEVKLSDFKGKKVYLKFWASWCGPCKKSM}$ PELMELAAKPDRDFEILTVIAPGIQGEKTVEQFPQWFQEQGYKDIPVLYDTKATTSKLIKFEAFLQNI

SP028 nucleotide (SEQ ID NO:41)

GACTTTTAACAATAAAACTATTGAAGAGTTGCACAATCTCCTTGTCTCTAAGGAAATTTCTGCAACAGA ATTGACCCAAGCAACACTTGAAAATATCAAGTCTCGTGAGGAAGCCCTCAATTCATTTGTCACCATCGC TGAGGAGCAAGCTCTTGTTCAAGCTAAAGCCATTGATGAAGCLGGAATTGATGCTGACAATGTCCTTTC AGGAATTCCACTTGCTGTTAAGGATAACATCTCTACAGACGGTATTCTCACAACTGCTGCCTCAAAAAT GCTCTACAACTATGAGCCAATCTTTGATGCGACagCTgTTGCCAATGCAAAAACCAAGGGCATGATTGT CGTTGGAAAGACCAACATGGACGAATTTGCTATGGGTGGTTCAGGLGAAACTTCACACTACGGAGCAAC TAAAAACGCTTGGAACCACAGCAAGGTTCCTGGTGGGTCATCAAGTGGTTCTGCCGCAGCTGTAGCCTC AGGACAAGTTCGCTTGTCACTTGGTTCTGATACTGGTGGTTCCATCCGCCAACCTGCTGCCTTCAACGG AATCGTTGGTCTCAAACCAACCTACGGAACAGTTTCACGTTTCGGTCTCATTGCCTTTGGTAGCTCATT AGACCAGATTGGACCTTTTGCTCCTACTGTTAAGGAAAATGCCCTCTTGCTCAACGCTATTGCCAGCGA AGATGCTAAAGACTCTACTTCTGCTCCTGTCCGCATCGCCGACTTTACTTCAAAAAATCGGCCAAGACAT CAAGGGTATGAAAATCGCTTTGCCTAAGGAATACCTAGGCGAAGGAATTGATCCAGAGGTTAAGGAAAC AATCTTAAACGCGGCCAAACACTTTGAAAAATTGGGTGCTATCGTCGAAGAAGTCAGCCTTCCTCACTC TAAATACGGTGTTGCCGTTTATTACATCGCTTCATCAGAAGCTTCATCAAACTTGCAACGCTTCGA $\verb|CCAAGGTTTTGGTGAAGAGGTAAAACGTCGTATCATGCTGGGTACTTTCAGTCTTTCATCAGGTTACTA|\\$ TGATGCCTACTACAAAAAGGCTGGTCAAGTCCGTACCCTCATCATTCAAGATTTCGAAAAAGTCTTCGC GGATTACGATTTGGGTTCCAACTGCTCCAAGTGTTGCCTATGACTTGGATTCTCTCAACCATGA CCCAGTTGCCATGTACTTAGCCGACCTATTGACCATACCTGTAAACTTGGCAGGACTGCCTGGAATTTC TGGAGGTGACAAC

SP028 amino acid (SEQ ID NO:42)

TFNNKTIEELHNLLVSKEISATELTQATLENIKSREEALNSFVTIAEEQALVQAKAIDEAGIDADNVLS GIPLAVKDNISTDGILTTAASKMLYNYEPIFDATAVANAKTKGMIVVGKTNMDEFAMGGSGETSHYGAT KNAWNHSKVPGGSSSGSAAAVASGQVRLSLGSDTGGSIRQPAAFNGIVGLKPTYGTVSRFGLIAFGSSL DQIGPFAPTVKENALLLNAIASEDAKDSTSAPVRIADFTSKIGQDIKGMKIALPKEYLGEGIDPEVKET ILNAAKHFEKLGAIVEEVSLPHSKYGVAVYYIIASSEASSNLQRFDGIRYGYRAEDATNLDEIYVNSRS QGFGEEVKRRIMLGTFSLSSGYYDAYYKKAGQVRTLIIQDFEKVFADYDLILGPTAPSVAYDLDSLNHD PVAMYLADLLTIPVNLAGLPGISIPAGFSQGLPVGLQLIGPKYSEETIYQAAAAFEATTDYHKQQPVIF GGDN

57

SP030 nucleotide (SEQ ID NO:43)

SP030 amino acid (SEQ ID NO:44)

FTGKQLQVGDKALDFSLTTTDLSKKSLADFDGKKKVLSVVPSIDTGICSTQTRRFNEELAGLDNTVVLT VSMDLPFAQKRWCGAEGLDNAIMLSDYFDHSFGRDYALLINEWHLLARAVFVLDTDNTIRYVEYVDNIN SEPNFE

SP031 nucleotide (SEQ ID NO:45)

CCAGGCTGATACAAGTATCGCAGACATTCAAAAAAGAGGCGAACTGGTTGTCGGTGTCAAACAAGACGT
TCCCAATTTTGGTTACAANGATCCCAAGACCGGTACTTATTCTGGTATCGAAACCGACTTGGCCAAGAT
GGTAGCTGATGAACTCAAGGTCAAGATTCGCTATGTGCCGGTTACAGCACAAACCCGCGGCCCCCTTCT
AGACAATGAACAGGTCGATATGGATATCGCGACCTTTACCATCACGGACGACGCAAAAAACTCTACAA
CTTTACCAGTCCCTACTACACAGACGCTTCTGGATTTTTGGTCAATAAATCTGCCAAAATCAAAAAAGAT
TGAGGACCTAAACGGCAAAACCATCGGAGTCGCCCAAGGTTCTATCACCCAACGCCTGATTACTGAACT
GGGTAAAAAGAAAGGTCTGAAGTTTAAATTCGTCGAACTTGGTTCCTACCCAGAATTGATTACTTCCCT
GCACGCTCATCGTATCGATACCTTTTCCGTTGACCGCTCTATTCTATCTGGCTACACTAGTAAACGGAC
AGCACTACTAGATGATAACTTGGTTACTAAATGGAGCAAGGATTGTTACCAAGAAATCAAATACAGAGCT
CAACGACTATCTTGATAACTTGGTTACTAAATGGAGCAAGGATGGTAGTTTGCAGAAACCTTTATGACCG
TTACAAGCTCAAACCATCTAGCCATACTGCAGAT

SP031 amino acid (SEQ ID NO:46)

QADTSIADIQKRGELVVGVKQDVPNFGYXDPKTGTYSGIETDLAKMVADELKVKIRYVPVTAQTRGPLL DNEQVDMDIATFTITDERKKLYNFTSPYYTDASGFLVNKSAKIKKIEDLNGKTIGVAQGSITQRLITEL GKKKGLKFKFVELGSYPELITSLHAHRIDTFSVDRSILSGYTSKRTALLDDSFKPSDYGIVTKKSNTEL NDYLDNLVTKWSKDGSLQKLYDRYKLKPSSHTAD

SP032 nucleotide (SEQ ID NO:47)

GTCTGTATCATTTGAAAACAAAGAAACCATGGTGTCTTTGACTTTCACTATCTCTCAAGACCAAAT CAAACCAGAATTGGACCGTGTCTTCAAGtCAGTGAAGAAATCTCTTAATGTTCCAGGTTTCCGTAAAGG TCACCTTCCACGCCCTATCTTCGACCAAAAATTTGGTGAAGAAGCTCTTTATCAAGATGCAATGAACGC TGACGTAACTTCAATGGAAAAAGGTCAAGACTGGGTTATCACTGCTGAAGTCGTTACAAAACCTGAAGT AAAATTGGGTGACTACAAAAACCTTGAAGTATCAGTTGATGTAGAAAAAGAAGTAACTGACGCTGATGT CGAAGAGCGTATCGAACGCGAACGCAACACCTGGCTGAATTGGTTATCAAGGAAGCTGCTGCTGAAAA $\tt CGGCGACACTGTTGTGATCGACTTCGTTGGTTCTATCGACGGTGTTGAATTTGACGGTGGAAAAGGTGA$ AAACTTCTCACTTGGACTTGGTTCAGGTCAATTCATCCCTGGTTTCGAAGACCAATTGGTAGGTCACTC AGCTGGCGAAACCGTTGATGTTATCGTAACATTCCCAGAAGACTACCAAGCAGAAGACCTTGCAGGTAA AGAAGCTAAATTCGTGACAACTATCCACGAAGTAAAAGCTAAAGAAGTTCCGGCTCTTGACGATGAACT TGCTGCTAAAGAAGAAGCTTACAAAGATGCAGTTGAAGGTGCAGCAATTGATACAGCTGTAGAAAATGC TGAAATCGTAGAACTTCCAGAAGAAATGATCCATGAAGAAGTTCACCGTTCAGTAAATGAATTCCTTGG GAATTTGCAACGTCAAGGGATCAACCCTGACATGTACTTCCAAATCACTGGAACTACTCAAGAAGACCT TCACAACCAATACCAAGCAGAAGCTGAGTCACGTACTAAGACTAACCTTGTTATCGAAGCAGTTGCCAA AGCTGAAGGATTTGATGCTTCAGAAGAAGAAATCCAAAAAGAAGTTGAGCAATTGGCAGCAGACTACAA

CATGGAAGTTGCACAAGTTCAAAACTTGCTTTCAGCTGACATGTTGAAACATGATATCACTATCAAAAA AGCTGTTGAATTGATCACAAGCACAGCAACAGTAAAA

58

SP032 amino acid (SEQ ID NO:48)

SVSFENKETNRGVLTFTISQDQIKPELDRVFKSVKKSLNVPGFRKGHLPRPIFDQKFGEEALYQDAMNA
LLPNAYEAAVKEAGLEVVAQPKIDVTSMEKGQDWVITAEVVTKPEVKLGDYKNLEVSVDVEKEVTDADV
EERIERERNNLAELVIKEAAAENGDTVVIDFVGSIDGVEFDGGKGENFSLGLGSGQFIPGFEDQLVGHS
AGETVDVIVTFPEDYQAEDLAGKEAKFVTTIHEVKAKEVPALDDELAKDIDEEVETLADLKEKYSKELA
AAKEEAYKDAVEGAAIDTAVENAEIVELPEEMIHEEVHRSVNEFLGNLQRQGINPDMYFQITGTTQEDL
HNQYQAEAESRTKTNLVIEAVAKAEGFDASEEEIQKEVEQLAADYNMEVAQVQNLLSADMLKHDITIKK
AVELITSTATVK

SP033 nucleotide (SEQ ID NO:49)

TGGTCAAAAGGAAAGTCAGACAGGAAAGGGGATGAAAATTGTGACCAGTTTTTATCCTATCTACGCTAT
GGTTAAGGAAGTATCTGGTGACTTGAATGATGTTCCGGATGATTCAGTCAAGTAGTGGTATTCACTCCTT
TGAACCTTCGGCAAATGATATCGCAGCCATCTATGATGCAGATGTCTTTGTTTACCATTCTCATACACT
CGAATCTTGGGCAGGAAGTCTGGATCCAAATCTAAAAAAATCCAAAGTGAAGGTCTTAGAGGCTTCTGA
GGGAATGACCTTGGAACGTGTCCCTGGACTAGAGGATGTGGAAGCAGGGGATGGAGTTGATGAAAAAAAC
GCTCTATGACCCTCACACATGGCTAGATCCTGAAAAAAGCTGGAGAAGAAGCCCAAATTATCGCTGATAA
ACTTTCAGAGGTGGATAGTGAGCATAAAGAGACTTATCAAAAAAATGCGCAACCTTTATCAAAAAAAGCT
CAGGAAT

SP033 amino acid (SEQ ID NO:50)

GQKESQTGKGMKIVTSFYPIYAMVKEVSGDLNDVRMIQSSSGIHSFEPSANDIAAIYDADVFVYHSHTL ESWAGSLDPNLKKSKVKVLEASEGMTLERVPGLEDVEAGDGVDEKTLYDPHTWLDPEKAGEEAQIIADK LSEVDSEHKETYQKNAQPLSKKLRN

SP034 nucleotide (SEQ ID NO:51)

GAAGGATAGATATATTTTAGCATTTGAGACATCCTGTGATGAGACCAGTGTCGCCGTCTTGAAAAAACGA
CGATGAGCTCTTGTCCAATGTCATTGCTAGTCAAATTGAGAGTCACAAACGTTTTGGTGGCGTAGTGCC
CGAAGTAGCCAGTCGTCACCATGTCGAGGTCATTACAGCCTGTATCGAGGAGGCATTGGCAGAAGCAGG
GATTACCGAAGAGGACGTGACAGCTGTTGCGGTTACCTACGGACCAGGCTTGGTCGGAGCCTTGCTAGT
TGGTTTGTCAGCTGCCAAGGCCTTTGCTTGGGCTCACGGACTTCCACTGATTCCTGTTAATCACATGGC
TGGGCACCTCATGGCAGCTCAGAGTGTGGAGCCTTTGGAGTTTCCCTTGCTAGCCCTCTTGGTCAGCGG
CGGACACACAGAGTTGGTTTATGTTTCGGAGGCAGGAGTTATAAAGATTGTTGGGGAAAACCCGTGATGA
TGCGGTTGGTGAGGCTTATGATAAGGTCGGCCGTGTCATGGGCTTGACCTATCCTGCAGGTCGTGAGAT
TGACGAGCTGGCTCATCAGGGGCAGGATATTTATGATTTCCCCCGTGCCATGATTAAAGGAAGATAATCT
GGAGTTCTCCTTCCAGGTTTGAAAATCTGCCTTTATCAATCTTCATCACAATGCCGAGCAAAAAGGAAAA
CCAAGAAGGCTTTGGAGAAATATCCTGTTAAAAATCCTAGTTGTGGCAGGTGTGTGGCAGCCAATAAAGG
TCTCAGAGAACCCTAGCAGCCGAAATCACAGATGTCAAGGTTATCACCCCCCTCTGCGACCTCTGCGG
AGACAATGCAGGTATGATTGCCTATGCCAGCGTCAGCNAGTGGAACAAAAACTTCGCAGGCTGGGA
CCTCAATGCCAAACCAAGTCTTGCCTTTGATACCATGGAA

SP034 amino acid (SEQ ID NO:52)

KDRYILAFETSCDETSVAVLKNDDELLSNVIASQIESHKRFGGVVPEVASRHHVEVITACIEEALAEAG ITEEDVTAVAVTYGPGLVGALLVGLSAAKAFAWAHGLPLIPVNHMAGHLMAAQSVEPLEFPLLALLVSG GHTELVYVSEAGDYKIVGETRDDAVGEAYDKVGRVMGLTYPAGREIDELAHQGQDIYDFPRAMIKEDNL EFSFSGLKSAFINLHHNAEQKGESLSTEDLCASFQAAVMDILMAKTKKALEKYPVKILVVAGGVAANKG LRERLAAEITDVKVIIPPLRLCGDNAGMIAYASVSXWNKENFAGWDLNAKPSLAFDTME

SP035 nucleotide (SEQ ID NO:53)

GGTAGTTAAAGTTGGTATTAACGGTTTCGGACGTATCGGTCGTCTTGCTTTCCGTCGTATCCAAAACGT AGAAGGTGTTGAAGTTACACGCATCÄACGACCTTACAGATCCAGTTATGCTTGCACACTTGTTGAAATA CGACACAACTCAAGGTCGTTTCGACGGTACTGTTGAAGTTAAAGAAGGTGGATTTGAAGTTAACGGTAA ATTCATCAAAGTTTCTGCTGAACGTGATCCAGAACAAATCGACTGGCTACTGACGGTGTAGAAATCGT TCTTGAAGCTACTGGTTTCTTTGCTAAGAAAGAAGCAGCTGAAAAACACCTTAAAGGTGGAGCTAAAAA

AGTTGTTATCACTGCTCCTGGTGGAAACGACGTTAAAACAGTTGTATTCAACACTAACCACGACGTTCT
TGACGGTACTGAAACAGTTATCTCAGGTGCTTCATGTACTACAAACTGCTTGGCTCCAATGGCTAAAGC
TCTTCAAGACAACTTTGGTGTTGTTGAAGGATTGATGACTACTACCACGCTTACACTGGTGACCAAAT
GATCCTTGACGGACCACACCGTGGTGGTGACCTTCGCCGTGCTCGCGCTGGTGCTGCAAACATCGTTCC
TAACTCAACTGGTGCTGCAAAAGCTATCGGTCTTGTAATCCCAGAATTGAATGGTAAACTTGACGGATC
TGCACAACGCGTTCCAACTCCAACTGGATCAGTTACTGAATTGGTAGCAGTTCTTGAAAAGAACGTTAC
TGTTGATGAAGTGAACGCAGCTATGAAAGCAGCTTCAAACGAATCATACGGTTACACAGAAGATCCAAT
CGTATCTTCAGATATCGTAGGTATGTTTACGGTTCATTGTTTGACGCAAACTCAAACTAAAGTTCTTGA
CGTTGACGGTAAACAATTGGTTAAAGTTGTATCATGGTACGACAACGAAATGTCATACACTGCACAACT
TGTTCGTACTCTTGGAATACTTCGCAAAAAATTGC

59

SP035 amino acid (SEQ ID NO:54)

VVKVGINGFGRIGRLAFRRIQNVEGVEVTRINDLTDPVMLAHLLKYDTTQGRFDGTVEVKEGGFEVNGK FIKVSAERDPEQIDWATDGVEIVLEATGFFAKKEAAEKHLKGGAKKVVITAPGGNDVKTVVFNTNHDVL DGTETVISGASCTTNCLAPMAKALQDNFGVVEGLMTTIHAYTGDQMILDGPHRGGDLRRARAGAANIVP NSTGAAKAIGLVIPELNGKLDGSAQRVPTPTGSVTELVAVLEKNVTVDEVNAAMKAASNESYGYTEDPI VSSDIVGMSYGSLFDATQTKVLDVDGKQLVKVVSWYDNEMSYTAQLVRTLGILRKNC

SP036 nucleotide (SEQ ID NO:55)

TTCTTACGAGTTGGGACTGTATCAAGCTAGAACGGTTAAGGAAAATAATCGTGTTTCCTATATAGATGG AAAACAAGCGACGCAAAAAACGGAGAATTTGACTCCTGATGAGGTTAGCAAGCGTGAAGGAATCAATGC TGAGCAAATCGTCATCAAGATAACAGACCAAGGCTATGTCACTTCACATGGCGACCACTATCATTATTA CAATGGTAAGGTTCCTTATGACGCTATCATCAGTGAAGAATTACTCATGAAAGATCCAAACTATAAGCT AAAAGATGAGGATATTGTTAATGAGGTCAAGGGTGGATATGTTATCAAGGTAGATGGAAAATACTATGT GCATAGTCAACATCGTGAAGGTGGAACTCCAAGAAACGATGGTGCTGTTGCCTTGGCACGTTCGCAAGG ACGCTATACTACAGATGATGGTTATATCTTTAATGCTTCTGATATCATAGAGGATACTGGTGATGCTTA TATCGTTCCTCATGGAGATCATTACCATTACATTCCTAAGAATGAGTTATCAGCTAGCGAGTTGGCTGC TGCAGAAGCCTTCCTATCTGGTCGAGGAAATCTGTCAÀATTCAAGAACCTATCGCCGACAAAATAGCGA TAACACTTCAAGAACAAACTGGGTACCTTCTGTAAGCAATCCAGGAACTACAAATACTAACACAAGCAA ${\tt CAACAGCAACACTAACAGTCAAGCAAGTCAAAGTAATGACATTGATAGTCTCTTGAAACAGCTCTACAA}$ ACTGCCTTTGAGTCAACGACATGTAGAATCTGATGGCCTTGTCTTTGATCCAGCACAAATCACAAGTCG AACAGCTAGAGGTGTTGCAGTGCCACACGGAGATCATTACCACTTCATCCCTTACTCTCAAATGTCTGA ATTGGAAGAACGAATCGCTCGTATTATTCCCCTTCGTTATCGTTCAAACCATTGGGTACCAGATTCAAG GCCAGAACAACCAAGTCCACAACCGACTCCGGAACCTAGTCCAGGCCCGCAACCTGCACCAAATCTTAA AATAGACTCAAATTCTTCTTTGGTTAGTCAGCTGGTACGAAAAGTTGGGGAAGGATATGTATTCGAAGA AAAGGGCATCTCTCGTTATGTCTTTGCGAAAGATTTACCATCTGAAACTGTTAAAAATCTTGAAAGCAA GTTATCAAAACAAGAGAGTGTTTCACACACTTTAACTGCTAAAAAAAGAAAATGTTGCTCCTCGTGACCA AGAATTTTATGATAAAGCATATAATCTGTTAACTGAGGCTCATAAAGCCTTGTTTGNAAATAAGGGTCG ATTGGTAGATGATTTATTGGCATTCCTAGCACCAATTACCCATCCAGAGCGACTTGGCAAACCAAATTC TCAAATTGAGTATACTGAAGACGAAGTTCGTATTGCTCAATTAGCTGATAAGTATACAACGTCAGATGG TTACATTTTGATGAACATGATATAATCAGTGATGAAGGAGATGCATATGTAACGCCTCATATGGGCCA TAGTCACTGGATTGGAAAAGATAGCCTTTCTGATAAGGAAAAAGTTGCAGCTCAAGCCTATACTAAAGA AAAAGGTATCCTACCTCCAGCCGCAGATGTTAAAGCAAATCCAACTGGAGATAGTGCAGCAGC TATTTACAATCGTGTGAAAGGGGAAAAACGAATTCCACTCGTTCGACTTCCATATATGGTTGAGCATAC AGTTGAGGTTAAAAACGGTAATTTGATTATTCCTCATAAGGATCATTACCATAATATTAAATTTGCTTG AGGCAAGAAGACCACAGTGAAGATCCAAATAAGAACTTCAAAGCGGATGAAGAGCCAGTAGAGGAAAC ACCTGCTGAGCCAGAAGTCCCTCAAGTAGAGACTGAAAAAGTAGAAGCCCAACTCAAAGAAGCAGAAGT TTTGCTTGCGAAAGTAACGGATTCTAGTCTGAAAGCCAATGCAACAGAAACTCTAGCTGGTTTACGAAA TAATTTGACTCTTCAAATTATGGATAACAATAGTATCATGGCAGAAGCAGAAAAATTACTTGCGTTGTT AAAAGGAAGTAATCCTTCATCTGTAAGTAAGGAAAAAATAAAC

SP036 amino acid (SEQ ID NO:56)

SYELGLYQARTVKENNRVSYIDGKQATQKTENLTPDEVSKREGINAEQIVIKITDQGYVTSHGDHYHYY NGKVPYDAIISEELLMKDPNYKLKDEDIVNEVKGGYVIKVDGKYYVYLKDAAHADNVRTKEEINRQKQE WO 98/18930

Table 1 60

HSQHREGGTPRNDGAVALARSQGRYTTDDGYIFNASDIIEDTGDAYIVPHGDHYHYIPKNELSASELAA AEAFLSGRGNLSNSRTYRRQNSDNTSRTNWVPSVSNPGTTNTNTSNNSNTNSQASQSNDIDSLLKQLYK LPLSQRHVESDGLVFDPAQITSRTARGVAVPHGDHYHFIPYSQMSELEERIARIIPLRYRSNHWVPDSR PEQPSPQPTPEPSPGPQPAPNLKIDSNSSLVSQLVRKVGEGYVFEEKGISRYVFAKDLPSETVKNLESK LSKQESVSHTLTAKKENVAPRDQEFYDKAYNLLTEAHKALFXNKGRNSDFQALDKLLERLNDESTNKEK LVDDLLAFLAPITHPERLGKPNSQIEYTEDEVRIAQLADKYTTSDGYIFDEHDIISDEGDAYVTPHMGH SHWIGKDSLSDKEKVAAQAYTKEKGILPPSPDADVKANPTGDSAAAIYNRVKGEKRIPLVRLPYMVEHT VEVKNGNLIIPHKDHYHNIKFAWFDDHTYKAPNGYTLEDLFATIKYYVEHPDERPHSNDGWGNASEHVL GKKDHSEDPNKNFKADEEPVEETPAEPEVPQVETEKVEAQLKEAEVLLAKVTDSSLKANATETLAGLRN NLTLQIMDNNSIMAEAEKLLALLKGSNPSSVSKEKIN

SP038 nucleotide (SEQ ID NO:57)

TACTGAGATGCATCATAATCTAGGAGCTGAAAAGCGTTCAGCAGTGGCTACTACTATCGATAGTTTTAA GGAGCGAAGTCAAAAAGTCAGAGCACTATCTGATCCAAATGTGCGTTTTGTTCCCTTCTTTGGCTCTAG TGAATGGCTTCGTTTTGACGGTGCTCATTCTGCGGTATTAGCTGAGAAATACAATCGTTCCTACCGTCC TTATCTTTTAGGACAGGGGGGAGCTGCATCGCTTAACCAATATTTTGGAATGCAACAGATGTTACCACA GCTGGAGAATAAACAAGTTGTGTATGTTATCTCACCTCAGTGGTTCAGTAAAAATGGCTATGATCCAGC AGCCTTCCAGCAGTATTTTAATGGAGACCAGTTGACTAGTTTTCTGAAACATCAATCTGGGGATCAGGC TAGTCAATATGCAGCGACTCGCTTACTGCAACAGTTCCCAAACGTAGCTATGAAGGACCTGGTTCAGAA GTTGGCAAGTAAAGAAGAATTGTCGACAGCAGACAATGAAATGATTGAATTATTGGCTCGTTTTAATGA ACGCCAAGCTTCCTTTTTTGGTCAGTTTTCGGTTAGAGGCTATGTTAACTACGATAAGCATGTAGCTAA GTATTTAAAAATCTTGCCAGACCAGTTTTCTTATCAGGCAATAGAAGATGTTGTCAAAGCAGATGCTGA AAAAAATACTTCCAATAATGAGATGGGAATGGAAAATTATTTCTATAATGAGCAGATCAAGAAGGATTT GAAGAAATTAAAGGATTCTCAGAAAAGCTTTACCTATCTCAAGTCGCCAGAGTATAATGNNTTGCAGTT GGTTTTAACACAGTTTTCTAAATCTAAGGTAAACCCGATTTTTATCATTCCACCTGTTAATAAAAAATG GATGNACTATGCTGGTCTACGAGAGGATATGTACCAACAAACGGTGCAGAAGATTCGCTACCAGTTAGA CATTCACCTTGGTTGGGTTGGTTGGCTTTTGACAAGGCAGTTGATCCTTTCCTATCCAATCCCAC ACCAGCTCCGACTTACCATCTGAATGAGCGCTTTTTCAGCAAAGATTGGGCGACTTATGATGGAGATGT CAAAGAA

SP038 amino acid (SEQ ID NO:58)

TEMHHNLGAEKRSAVATTIDSFKERSQKVRALSDPNVRFVPFFGSSEWLRFDGAHSAVLAEKYNRSYRP YLLGQGGAASLNQYFGMQQMLPQLENKQVVYVISPQWFSKNGYDPAAFQQYFNGDQLTSFLKHQSGDQA SQYAATRLLQQFPNVAMKDLVQKLASKEELSTADNEMIELLARFNERQASFFGQFSVRGYVNYDKHVAK YLKILPDQFSYQAIEDVVKADAEKNTSNNEMGMENYFYNEQIKKDLKKLKDSQKSFTYLKSPEYNXLQL VLTQFSKSKVNPIFIIPPVNKKWMXYAGLREDMYQQTVQKIRYQLESQGFTNIADFSKDGGEPFFMKDT IHLGWLGWLAFDKAVDPFLSNPTPAPTYHLNERFFSKDWATYDGDVKE

SP039 nucleotide (SEQ ID NO:59)

GGTTTTGAGAAAGTATTTGCAGGGGGCCCTGATTGAGTCGATTGAGCAAGTGGAAAATGACCGTATTGT GGAAATTACAGTTTCCAATAAAAACGAGATTGGAGACCATATCCAGGCTACCTTGATTATCGAAATTAT GGGGAAACACAGTAATATTCTACTGGTCGATAAAAGCAGTCATAAAATCCTCGAAGTTATCAAACACGT CGGCTTTTCACAAAATAGCTACCGCACCTTACTTCCAGGATCGACCTATATCGCTCCGCCAAGTACAAA ATCTCTCAATCCTTTTACTATCAAGGATGAAAAGCTCTTTGAAATCCTGCAAACCCAAGAACTAACAGC AAAAAATCTTCAAAGCCTCTTTCAAGGTCTGGGACGCGATACGGCAAATGAATTGGAAAGGATACTGGT CTTCAGTCCAGTTCCTTTTGCAAATCAGGTGGGAGAGCCTTTTGCAAATCTTTCTGATTTGTTGGACAC CTACTATAAGGATAAGGCTGAGCGCGACCGCGTCAAACAGCAGGCCAGTGAACTGATTCGTCGTGTTGA TGAAGAATTTCGTCAAAAAGGAGAATTGCTGACAACCTTCCTCCACCAAGTGCCTAACGACCAAGACCA GGTTATCCTAGACAACTACTATACCAACCAACCTATCATGATTGCGCTTGATAAGGCTCTGACTCCCAA CCAGAATGCCCAACGCTATTTTAAACGGTATCAGAAACTCAAAGAAGCTGTCAAATACTTGACTGATTT GATTGAAGAACCAAAGCCACTATTCTCTATCTGGAAAGTGTAGAAACCGTCCTCAACCAAGCTGGACT GGAAGAAATCGCTGAAATCCGTGAAGAATTGATTCAAACAGGTTTTATCCGCAGAAGACAACGGGAGAA AATCCAGAAACGCAAAAAACTAGAACAATATCTAGCAAGCGATGGCAAAACCATCATCTATGTCGGACG AAACAATCTTCAAAATGAGGAATTGACCTTTAAAATGGCCCGCAAGGAGGAACTTTGGTTCCATGCTAA

AGCAGAGTTAGCTGCCTACTTCTCTCAAGGGCGCCTGTCGAATCTGGTGCAGGTAGATATGATTGAAGT CAAAAAACTCAATAAACCAACTGGTGGAAAACCCGGCTTTGTCACTTACACAGGACAAAAGACCCTCCG CGTCACACCAGACTCCAAAAAAATTGCATCCATGAAAAAATCC

SP039 amino acid (SEQ ID NO:60)

VLRKYLQGALIESIEQVENDRIVEITVSNKNEIGDHIQATLIIEIMGKHSNILLVDKSSHKILEVIKHV GFSQNSYRTLLPGSTYIAPPSTKSLNPFTIKDEKLFEILQTQELTAKNLQSLFQGLGRDTANELERILV SEKLSAFRNFFNQETKPCLTETSFSPVPFANQVGEPFANLSDLLDTYYKDKAERDRVKQQASELIRRVE NELQKNRHKLKKQEKELLATDNAEEFRQKGELLTTFLHQVPNDQDQVILDNYYTNQPIMIALDKALTPN QNAQRYFKRYQKLKEAVKYLTDLIEETKATILYLESVETVLNQAGLEEIAEIREELIQTGFIRRRQREK IQKRKKLEQYLASDGKTIIYVGRNNLQNEELTFKMARKEELWFHAKDIPGSHVVISGNLDPSDAVKTDA AELAAYFSQGRLSNLVQVDMIEVKKLNKPTGGKPGFVTYTGQKTLRVTPDSKKIASMKKS

SP040 nucleotide (SEQ ID NO:61)

SP040 amino acid (SEQ ID NO:62)

TTFTIHTVESAPAEV,KEILETVEKDNNGYIPNLIGLLANAPTVLEAYQIVSSIHRRNSLTPVEREVVQI TAAVTNGCAFCVAGHTAFSIKQIQMNDDLIQALRNRTPIETDPKLDTLAKFTLAVINTKGRVGDEALSE FLEAGYTQQNALDVVFGVSLAILCNYANNLANTPINPELQPYA

SP041 nucleotide (SEQ ID NO:63)

SP041 amino acid (SEQ ID NO:64)

AKERVDVLAYKQGLFETREQAKRGVMAGLVVAVLNGERFDKPGEKIPDDTELKLKGEKLKYVSRGGLKL EKALQVFDLSVDGATTIDIGASTGGFTDVMLQNSAKLVFAVDVGTNQLAWKLRQDPRVVSMEQFNFRYA EKTDFEQEPSFASIDVSFISLSLILPALHRVLADQGQVVALVKPQFEAGREQIGKNGIIRDAKVHQNVL ESVTAMAVEVGFSVLGLDFSPIQGGHGNIEFLAYLKKEKSASNQILAEIKEAVERAHSQFKNE

SP042 nucleotide (SEQ ID NO:65)

WO 98/18930 PCT/US97/19422

62

AGAAGCCTATTGGAATGGGAAGCAGGGATCTCGTCCTTCTTCAAGTTCTAGTTATAATGCAAATCCAGC TCAACCAAGATTGTCAGAGAACCACAATCTGACTGTCACTCCAACTTATCATCAAAATCAAGGGGAAAA CATTTCAAGCCTTTTACGTGAATTGTATGCTAAACCCTTATCAGAACGCCATGTGGAATCTGATGGCCT TATTTTCGACCCAGCGCAAATCACAAGTCGAACCGCCAGAGGTGTAGCTGTCCCTCATGGTAACCATTA CCACTTTATCCCTTATGAACAAATGTCTGAATTGGAAAAACGAATTGCTCGTATTATTCCCCTTCGTTA TCGTTCAAACCATTGGGTACCAGATTCAAGACCAGAACCAAGTCCACAATCGACTCCGGAACCTAG TCCAAGTCCGCAACCTGCACCAAATCCTCAACCAGCTCCAAGCAATCCAATTGATGAGAAATTGGTCAA AGAAGCTGTTCGAAAAGTAGGCGATGGTTATGTCTTTGAGGAGAATGGAGTTTCTCGTTATATCCCAGC CAAGGATCTTTCAGCAGAAACAGCAGCAGGCATTGATAGCAAACTGGCCAAGCAGGAAAGTTTATCTCA TAAGCTAGGAGCTAAGAAAACTGACCTCCCATCTAGTGATCGAGAATTTTACAATAAGGCTTATGACTT ACTAGCAAGATTCACCAAGATTTACTTGATAATAAAGGTCGACAAGTTGATTTTGAGGCTTTGGATAA CCTGTTGGAACGACTCAAGGATGTCNCAAGTGATAAAGTCAAGTTAGTGGANGATATTCTTGCCTTCTT AGCTCCGATTCGTCATCCAGAACGTTTAGGAAAACCAAATGCGCAAATTACCTACACTGATGATGAGAT ${\tt TCAAGTAGCCAAGTTGGCAGGCAAGTACACAACAGAAGACGGTTATATCTTTGATCCTCGTGATATAAC}$ CAGTGATGAGGGGGATGCCTATGTAACTCCACATATGACCCATAGCCACTGGATTAAAAAAGATAGTTT GTCTGAAGCTGAGAGCGGCAGCCCAGGCTTATGCTAAAGAGAAAGGTTTGACCCCTCCTTCGACAGA CCATCAGGATTCAGGAAATACTGAGGCAAAAGGAGCAGAAGCTATCTACAACCGCGTGAAAGCAGCTAA GAAGGTGCCACTTGATCGTATGCCTTACAATCTTCAATATACTGTAGAAGTCAAAAACGGTAGTTTAAT CATACCTCATTATGACCATTACCATAACATCAAATTTGAGTGGTTTGACGAAGGCCTTTATGAGGCACC GCATTCAGATAATGGTTTTGGTAACGCTAGCGACCATGTTCAAAGAAACAAAAATGGTCAAGCTGATAC AGAGAAACCGCAAAGCGAGAAACCAGAGTCTCCAAAAACCAACAGAGGAACCAGAAGAATCACCAGAGGA ATCAGAAGAACCTCAGGTCGAGACTGAAAAGGTTGAAGAAAACTGAGAGAGGCTGAAGATTTACTTGG AAAAATCCAGGAT

SP042 amino acid (SEQ ID NO:66)

CSYELGRHQAGQVKKESNRVSYIDGDQAGQKAENLTPDEVSKREGINAEQXVIKITDQGYVTSHGDHYH YYNGKVPYDAIISEELLMKDPNYQLKDSDIVNEIKGGYVIKVNGKYYVYLKDAAHADNIRTKEEIKRQK QERSHNHNSRADNAVAAARAQGRYTTDDGYIFNASDIIEDTGDAYIVPHGDHYHYIPKNELSASELAAA EAYWNGKQGSRPSSSSSYNANPAQPRLSENHNLTVTPTYHQNQGENISSLLRELYAKPLSERHVESDGL IFDPAQITSRTARGVAVPHGNHYHFIPYEQMSELEKRIARIIPLRYRSNHWVPDSRPEQPSPQSTPEPS PSPQPAPNPQPAPSNPIDEKLVKEAVRKVGDGYVFEENGVSRYIPAKDLSAETAAGIDSKLAKQESLSH ${\tt KLGAKKTDLPSSDREFYNKAYDLLARIHQDLLDNKGRQVDFEALDNLLERLKDVXSDKVKLVXDILAFL}$ APIRHPERLGKPNAQITYTDDEIQVAKLAGKYTTEDGYIFDPRDITSDEGDAYVTPHMTHSHWIKKDSL SEAERAAAOAYAKEKGLTPPSTDHODSGNTEAKGAEAIYNRVKAAKKVPLDRMPYNLQYTVEVKNGSLI IPHYDHYHNIKFEWFDEGLYEAPKGYTLEDLLATVKYYVEHPNERPHSDNGFGNASDHVQRNKNGQADT NQTEKPSEEKPQTEKPEEETPREEKPQSEKPESPKPTEEPEESPEESEEPQVETEKVEEKLREAEDLLG KIOD

SP043 nucleotide (SEQ ID NO:67)

TTATAAGGGTGAATTAGAAAAAGGATACCAATTTGATGGTTGGGAAATTTCTGGTTTCGAAGGTAAAAA AGACGCTGGCTATGTTATTAATCTATCAAAAGATACCTTTATAAAACCTGTATTCAAGAAAATAGAGGA AACTAAGGATGTTACAGCTACAGTTCTTGATAAAAACAATATCAGTAGTAAATCAACTACTAACAATCC TAATAAG

SP043 amino acid (SEQ ID NO:68)

YKGELEKGYQFDGWEISGFEGKKDAGYVINLSKDTFIKPVFKKIEEKKEEENKPTFDVSKKKDNPQVNH SQLNESHRKEDLQREEHSQKSDSTKDVTATVLDKNNISSKSTTNNPNK

SP044 nucleotide (SEQ ID NO:69)

GAATGTTCAGGCTCAAGAAAGTTCAGGAAATAAAATCCACTTTATCAATGTTCAAGAAGGTGGCAGTGA TGCGATTATTCTTGAAAGCAATGGACATTTTGCCATGGTGGATACAGGAGAAGATTATGATTTCCCAGA TGGAAGTGATTCTCGCTATCCATGGAGAAGGAATTGAAACGTCTTATAAGCATGTTCTAACAGACCG TGTCTTTCGTCGTTTGAAGGAATTGGGTGTCCAAAAACTTGATTTTATTTTGGTGACCCATACCCACAG TGATCATATTGGAAATGTTGATGAATTACTGTCTACCTATCCAGTTGACCGAGTCTATCTTAAGAAATA

63

SP044 amino acid (SEQ ID NO:70)

NVQAQESSGNKIHFINVQEGGSDAIILESNGHFAMVDTGEDYDFPDGSDSRYPWREGIETSYKHVLTDR VFRRLKELGVQKLDFILVTHTHSDHIGNVDELLSTYPVDRVYLKKYSDSRITNSERLWDNLYGYDKVLQ TAAEKGVSVIQNITQGDAHFQFGDMDIQLYNYENETDSSGELKKIWDDNSNSLISVVKVNGKKIYLGGD LDNVHGAEDKYGPLIGKVDLMKFNHHHDTNKSNTKDFIKNLSPSLIVQTSDSLPWKNGVDSEYVNWLKE RGIERINAASKDYDATVFDIRKDGFVNISTSYKPIPSFQAGWHKSAYGNWWYQAPDSTGEYAVGWNEIE GEWYYFNQTGILLQNQWKKWNNHWFYLTDSGASAKNWKKIAGIWYYFNKENQMEIGWIQDKEQWYYLDV DGSMKTGWLQYMGQWYYFAPSGE

SP045 nucleotide (SEQ ID NO:71)

CTTGGGTGTAACCCATATCCAGCTCCTTCCAGTCTTGTCTACTACTTTGTCAATGAATTGAAAAACCA TGAACGCTTGTCTGACTACGCTTCAAGCAACAGCAACTACAACTGGGGATATGACCCTCAAAACTACTT CTCCTTGACTGGTATGTACTCAAGCGATCCTAAGAATCCAGAAAAACGAATCGCAGAATTTAAAAACCT CGATCTCTTTGAAGATTTGGAACCAAACTACTACCACTTTATGGATGCCGATGGCACACCTCGAACTAG CTTTGGTGGTGGACGCTTGGGGACAACCCACCATATGACCAAACGGCTCCTAATTGACTCTATCAAATA CCTAGTTGATACCTACAAAGTGGATGGCTTCCGTTTCGATATGATGGGAGACCATGACGCCGCTTCTAT CGAAGAAGCTTACAAGGCTGCACGCGCCCTCAATCCAAACCTCATCATGCTTGGTGAAGGTTGGAGAAC CTATGCCGGTGATGAAAACATGCCTACTAAAGCTGCTGACCAAGATTGGATGAAACATACCGATACTGT CGCTGTCTTTTCAGATGACATCCGTAACAACCTCAAATCTGGTTATCCAAACGAAGGTCAACCTGCCTT AGCTGACAGCCCTGGAGATGTCATCCAATACATCGCAGCCCATGATAACTTGACCCTCTTTGACATCAT TGCCCAGTCTATCAAAAAAGACCCAAGCAAGGCTGAGAACTATGCTGAAATCCACCGTCGTTTACGACT TGGAAATCTCATGGTCTTGACAGCTCAAGGAACTCCATTTATCCACTCCGGTCAGGAATATGGACGTAC GTTGCGTGATAAGGACGCAACCCATTTGACTATCCTTACTTCATCCATGACTCTTACGATTCTAGTGA TGCAGTCAACAAGTTTGACTGGACTAAGGCTACAGATGGTAAAGCTTATCCTGAAAATGTCAAGAGCCG TGACTATATGAAAGGTTTGATTGCCCTTCGTCAATCTACAGATGCCTTCCGACTTAAGAGTCTTCAAGA TATCAAAGACCGTGTCCACCTCATCACTGTCCCAGGCCAAAATGGTGTGGAAAAAGAGGGATGTAGTGAT TGGCTACCAAATCACTGCTCCAAACGGCGATATCTACGCAGTCTTTGTCAATGCGGATGAAAAAGCTCG CGAATTTAATTTGGGAACTGCCTTTGCACATCTAAGAAATGCGGAAGTTTTGGCAGATGAAAACCAAGC AGGACCAGTCGGAATTGCCAACCCGAAAGGACTTGAATGGACTGAAAAAGGCTTGAAATTGAATTGCCCT TACAGCTACTGTTCTTCGAGTCTCTCAAAATGGAACTAGCCATGAGTCAACTGCAGAAGAGAAACCAGA CTCAACCCCTTCCAAGCCTGAACATCAAAATGAAGCTTCTCACCCTGCACATCAAGACCCAGCTCCAGA AGCTAGACCTGATTCTACTAAACCAGATGCCAAAGTAGCTGATGCGGAAAATAAACCTAGCCAAGCTAC AGCTGATTCACAAGCTGAACAACCAGCACAAGAAGCACAAGCATCATCTGTAAAAGAAGCGGTTCGAAA CGAATCGGTAGAAAACTCTAGCAAGGAAAATATACCTGCAACCCCAGATAAACAAGCTGAA

SP045 nucleotide (SEQ ID NO:72)

LGVTHIQLLPVLSYYFVNELKNHERLSDYASSNSNYNWGYDPQNYFSLTGMYSSDPKNPEKRIAEFKNL INEIHKRGMGAILDVVYNHTAKVDLFEDLEPNYYHFMDADGTPRTSFGGGRLGTTHHMTKRLLIDSIKY LVDTYKVDGFRFDMMGDHDAASIEEAYKAARALNPNLIMLGEGWRTYAGDENMPTKAADQDWMKHTDTV

AVFSDDIRNNLKSGYPNEGQPAFITGGKRDVNTIFKNLIAQPTNFEADSPGDVIQYIAAHDNLTLFDII AQSIKKDPSKAENYAEIHRRLRLGNLMVLTAQGTPFIHSGQEYGRTKQFRDPAYKTPVAEDKVPNKSHL LRDKDGNPFDYPYFIHDSYDSSDAVNKFDWTKATDGKAYPENVKSRDYMKGLIALRQSTDAFRLKSLQD IKDRVHLITVPGQNGVEKEDVVIGYQITAPNGDIYAVFVNADEKAREFNLGTAFAHLRNAEVLADENQA GPVGIANPKGLEWTEKGLKLNALTATVLRVSQNGTSHESTAEEKPDSTPSKPEHQNEASHPAHQDPAPE ARPDSTKPDAKVADAENKPSQATADSQAEQPAQEAQASSVKEAVRNESVENSSKENIPATPDKQAE

64

SP046 nucleotide (SEQ ID NO:73)

TAGTGATGGTACTTGGCAAGGAAAACAGTATCTGAAAGAAGATGGCAGTCAAGCAGCAAATGAGTGGGT AAAGCAAGGTGACGACTATTTTTACCTCAAATCTGGTGGCTATATGGCCAAATCAGAATGGGTAGAAGA CAAGGGAGCCTTTTATTATCTTGACCAAGATGGAAAGATGAAAAGAAATGCTTGGGTAGGAACTTCCTA TGTTGGTGCAACAGGTGCCAAAGTAATAGAAGACTGGGTCTATGATTCTCAATACGATGCTTGGTTTTA TATCAAAGCAGATGGACAGCACGCAGAGAAAGAATGGCTCCAAATTAAAGGGAAGGACTATTATTTCAA ATCCGGTGGTTATCTACTGACAAGTCAGTGGATTAATCAAGCTTATGTGAATGCTAGTGGTGCCAAAGT ACAGCAAGGTTGGCTTTTTGACAAACAATACCAATCTTGGTTTTACATCAAAGAAAATGGAAACTATGC TGATAAAGAATGGATTTTCGAGAATGGTCACTATTATTATCTAAAATCCGGTGGCTACATGGCAGCCAA TGAATGGATTTGGGATAAGGAATCTTGGTTTTATCTCAAATTTGATGGGAAAATGGCTGAAAAAGAATG GATTTGGGATAAGGAATCTTGGTTTTACCTCAAATCTGATGGGAAAATAGCTGAAAAAAGAATGGGTCTA CGATTCTCATAGTCAAGCTTGGTACTACTTCAAATCTGGTGGCTACATGGCGAAAAATGAGACAGTAGA TGGTTATCAGCTTGGAAGCGATGGTAAATGGCTTGGAGGAAAAACTACAAATGAAAATGCTGCTTACTA TCAAGTAGTGCCTGTTACAGCCAATGTTTATGATTCAGATGGTGAAAAGCTTTCCTATATATCGCAAGG TAGTGTCGTATGGCTAGATAAGGATAGAAAAAGTGATGACAAGCGCTTGGCTATTACTATTTCTGGTTT GTCAGGCTATATGAAAACAGAAGATTTACAAGCGCTAGATGCTAGTAAGGACTTTATCCCTTATTATGA GAGTGATGGCCACCGTTTTTATCACTATGTGGCTCAGAATGCTAGTATCCCAGTAGCTTCTCATCTTTC TGATATGGAAGTAGGCAAGAAATATTATTCGGCAGATGGCCTGCATTTTGATGGTTTTAAGCTTGAGAA TCCCTTCCTTTTCAAAGATTTAACAGAGGCTACAAACTACAGTGCTGAAGAATTGGATAAGGTATTTAG TTTGCTAAACATTAACAATAGCCTTTTGGAGAACAAGGGCGCTACTTTTAAGGAAGCCGAAGAACATTA CCATATCAATGCTCTTTATCTCCTTGCCCATAGTGCCCTAGAAAGTAACTGGGGAAGAAGTAAAATTGC CAAAGATAAGAATAATTTCTTTGGCATTACAGCCTATGATACGACCCCTTACCTTTCTGCTAAGACATT TGATGATGTGGATAAGGGAATTTTAGGTGCAACCAAGTGGATTAAGGAAAATTATATCGATAGGGGAAG AACTTTCCTTGGAAACAAGGCTTCTGGTATGAATGTGGAATATGCTTCAGACCCTTATTGGGGCGAAAA AATTGCTAGTGTGATGAAAAATCAATGAGAAGCTAGGTGGCAAAGAT

SP046 amino acid (SEQ ID NO:74)

SDGTWQGKQYLKEDGSQAANEWVXDTHYQSWFYIKADANYAENEWLKQGDDYFYLKSGGYMAKSEWVED KGAFYYLDQDGKMKRNAWVGTSYVGATGAKVIEDWVYDSQYDAWFYIKADGQHAEKEWLQIKGKDYYFK SGGYLLTSQWINQAYVNASGAKVQQGWLFDKQYQSWFYIKENGNYADKEWIFENGHYYYLKSGGYMAAN EWIWDKESWFYLKFDGKMAEKEWVYDSHSQAWYYFKSGGYMTANEWIWDKESWFYLKSDGKIAEKEWVY DSHSQAWYYFKSGGYMAKNETVDGYQLGSDGKWLGGKTTNENAAYYQVVPVTANVYDSDGEKLSYISQG SVVWLDKDRKSDDKRLAITISGLSGYMKTEDLQALDASKDFIPYYESDGHRFYHYVAQNASIPVASHLS DMEVGKKYYSADGLHFDGFKLENPFLFKDLTEATNYSAEELDKVFSLLNINNSLLENKGATFKEAEEHY HINALYLLAHSALESNWGRSKIAKDKNNFFGITAYDTTPYLSAKTFDDVDKGILGATKWIKENYIDRGR TFLGNKASGMNVEYASDPYWGEKIASVMMKINEKLGGKD

SP048 nucleotide (SEQ ID NO:75)

SP048 amino acid (SEQ ID NO:76)

GIQYVRDDTRDKEEGIEYDDADNGDIIVKVATKPKVVTKKISSTRIRYEKDETKDRSENPVTIDGEDGY VTTTRTYDVNPETGYVTEQVTVDRKEATDTVIKVPAKSKVEEVLVPFATKYEADNDLSAGQEQEITLGK NGKTVTTITYNVDGKSGQVTESTLSQKKDSQTRVVKKRTXPQVLVQEIPIETEYLDGPTLDKSQEVEEV GEIGKLLLLQSILVDERDGTIEETTSRQITKEMVKRRIRRGTREPEKVVVPEQSSIPSYPVSVTSNQGT DVAVEPAKAVAPTTDWKQENGMWYFYNTDGSMATGWVQVNSSWYYLNSNGSMKVNQWFQVGGKWYYVNT SGELAVNTSIDGYRVNDNGEWVR

SP049 nucleotide (SEQ ID NO:77)

SP049 amino acid (SEQ ID NO:78)

DNREALKTFMTGENFYLQHYLGAHREELNGEHGYTFRVWAPNAQAVHLVGDFTNWIENQIPMVRNDFGV WEVFTNMAQEGHIYKYHVTRQNGHQLMKIDPFAVRYEARPGTGAIVTELPEKKWKDGLWLARRKRWGFE ERPVNIYEVHAGSWKRNSDGSPYSFAQLKDELIPYLVEMNYTHIEFMPLMSHPLGLSWGYQLMGYFALE HAYGRPEEFQDFV

SP050 nucleotide (SEQ ID NO:79)

SP050 amino acid (SEQ ID NO:80)

DFVEECHTHNIGVIVDWVPXHFTINDDALAYYDGTPTFEYQDHNKAHNHGWGALNFDLGKNEVQSFLIS CIKHWIDVYHLDGIRVDAVSNMLYLDYDDAPWTPNKDGGNLNYEGYYFLQRLNEVIKLEYPDVMMIAEE SSSAIKITGMKEIGGLGFDYKWNMGWMNDILRFYEEDPIYRKYDFNLVTFSFMYVXKENYLLPFSHDEV VHGKKSMMHKMWGDRYNQFAGLRNLYTYQICHPGKKLLFMGSEYGQFLEWKSEEQLEWSNLEDPMNAKM KYFASQLNQFYKDHRCLWEIDTSYDGIEIIDADNRDQSVLSFIRKGKKG

SP051 nucleotide (SEQ ID NO:81)

ATCTGTAGTTTATGCGGATGAAACACTTATTACTCATACTGCTGAGAAACCTAAAGAGGGAAAAAATGAT AGTAGAAGAAAAGGCTGATAAAGCTTTGGAAACTAAAAATATAGTTGAAAGGACAGAACAAAGTGAACC TAGTTCAACTGAGGCTATTGCATCTGAGNAGAAAGAAGATGAAGCCGTAACTCCAAAAGAGGAAAAAGT GTCTGCTAAACCGGAAGAAAAAGCTCCAAGGATAGAATCACAAGCTTCAAATCAAGAAAAACCGCTCAA GGAAGATGCTAAAGCTGTAACAAATGAAGAAGTGAATCAAATGATTGAAGACAGGAAAGTGGATTTTAA TCAAAATTGGTACTTTAAACTCAATGCAAATTCTAAGGAAGCCATTAAACCTGATGCAGACGTATCTAC GTGGAAAAATTAGATTTACCGTATGACTGGAGTATCTTTAACGATTTCGATCATGAATCTCCTGCACA AAATGAAGGTGGACAGCTCAACGGTGGGGAAGCTTGGTATCGCAAGACTTCAAACTAGATGAAAAAAA

66

CCTCAAGAAAATGTTCGCCTTACTTTTGATGGCGTCTACATGGATTCTCAAGTTTATGTCAATGGTCA GTTAGTGGGGCATTATCCAAATGGTTATAACCAGTTCTCATATGATATCACCAAATACCTTCAAAAAGA TGGTATCTATCGTGATGTGACTTTACAAGTGACAGATAAGGTGCATGTTGAGAAAAATGGGACAACTAT TTTAACACCAAAACTTGAAGAACAACAACATGGCAAGGTTGAAACTCATGTGACCAGCAAAATCGTCAA TACGGACGACAAAGACCATGAACTTGTAGCCGAATATCAAATCGTTGAACGAGGTGGTCATGCTGTAAC AGGCTTAGTTCGTACAGCGAGTCGTACCTTAAAAGCACATGAATCAACAAGCCTAGATGCGATTTTAGA AGTTGAAAGACCAAAACTCTGGACTGTTTTAAATGACAAACCTGCCTTGTACGAATTGATTACGCGTGT AAATGAAGGTTTCTCTTTGAATGGTGAACGTATTAAATTCCATGGAGTATCCTTGCACCACGACCATGG TAACTCCATCCGTACAACCCACAACCCTGCTAGTGAGCAAACCTTGCAAATCGCAGCAGAACTAGGTTT ACTCGTTCAGGAAGAGGCCTTTGATACGTGGTATGGTGGCAAGAAACCTTATGACTATGGACGTTTCTT TGAAAAAGATGCCACTCACCCAGAAGCTCGAAAAGGTGAAAAATGGTCTGATTTTGACCTACGTACCAT GGTCGAAAGAGCCAAAAACAACCCTGCTATCTTCATGTGGTCAATTGGTAATGAAATAGGTGAAGCTAA TGGTGATGCCCACTCTTTAGCAACTGTTAAACGTTTGGTTAAGGTTATCAAGGATGTTGATAAGACTCG CTATGTTACCATGGGAGCAGATAAATTCCGTTTCGGTAATGGTAGCGGAGGGCATGAGAAAATTGCTGA TGAACTCGATGCTGTTGGATTTAACTATTCTGAAGATAATTACAAAGCCCTTAGAGCTAAGCATCCAAA ATGGTTGATTTATGGATCAGAAACATCTTCAGCTACCCGTACACGTGGAAGTTACTATCGCCCTGAACG TGAATTGAAACATAGCAATGGACCTGAGCGTAATTATGAACAGTCAGATTATGGAAATGATCGTGTGGG TTGGGGGAAAACAGCAACCGCTTCATGGACTTTTGACCGTGACAACGCTGGCTATGCTGGACAGTTTAT CTGGACAGGTACGGACTATATTGGTGAACCTACACCATGGCACAACCAAAATCAAACTCCTGTTAAGAG CTCTTACTTTGGTATCGTAGATACAGCCGGCATTCCAAAACATGACTTCTATCTCTACCAAAAGC

SP051 amino acid (SEQ ID NO:82)

SVVYADETLITHTAEKPKEEKMIVEEKADKALETKNIVERTEQSEPSSTEAIASEXKEDEAVTPKEEKV SAKPEEKAPRIESQASNQEKPLKEDAKAVTNEEVNQMIEDRKVDFNQNWYFKLNANSKEAIKPDADVST WKKLDLPYDWSIFNDFDHESPAQNEGGQLNGGEAWYRKTFKLDEKDLKKNVRLTFDGVYMDSQVYVNGQ LVGHYPNGYNQFSYDITKYLQKDGRENVIAVHAVNKQPSSRWYSGSGIYRDVTLQVTDKVHVEKNGTTI LTPKLEEQQHGKVETHVTSKIVNTDDKDHELVAEYQIVERGGHAVTGLVRTASRTLKAHESTSLDAILE VERPKLWTVLNDKPALYELITRVYRDGQLVDAKKDLFGYRYYHWTPNEGFSLNGERIKFHGVSLHHDHG ALGAEENYKAEYRRLKQMKEMGVNSIRTTHNPASEQTLQIAAELGLLVQEEAFDTWYGGKKPYDYGRFF EKDATHPEARKGEKWSDFDLRTMVERGKNNPAIFMWSIGNEIGEANGDAHSLATVKRLVKVIKDVDKTR YVTMGADKFRFGNGSGGHEKIADELDAVGFNYSEDNYKALRAKHPKWLIYGSETSSATRTRGSYYRPER ELKHSNGPERNYEQSDYGNDRVGWGKTATASWTFDRDNAGYAGQFIWTGTDYIGEPTPWHNQNQTPVKS SYFGIVDTAGIPKHDFYLYQS

SP052 nucleotide (SEQ ID NO:83)

TTACTTTGGTATCGTAGATACAGCCGGCATTCCAAAACATGACTTCTATCTCTACCAAAGCCAATGGGT TTCTGTTAAGAAGAACCGATGGTACACCTTCTTCCTCACTGGAACTGGGAAAACAAAGAATTAGCATC CAAAGTAGCTGACTCAGAAGGTAAGATTCCAGTTCGTGCTTATTCGAATGCTTCTAGTGTAGAATTGTT AGAAGGTGCAAATGCTAATGAACTTTATCTTGAATGGAAAGTTGCCTATCAACCAGGTACCTTGGAAGC AATTGCTCGTGATGAATCTGGCAAGGAAATTGCTCGAGATAAGATTACGACTGCTGGTAAGCCAGCGGC AGTTCGTCTTATTAAGGAAGACCATGCGATTGCAGCAGATGGAAAAGACTTGACTTACATCTACTATGA TTCTTGGATTCGTAAAGCATTTAATGGTAAAGGTGTTGCCATTGTCAAATCAACTGAACAAGCAGGGAA AGGACAAGAGAAGACTGTTTTGGGGACAGAAGTGCCAAAAGTACAGACCATTATTGGAGAGGCACCTGA **Table 1** 67

AATGCCTACCACTGTTCCGTTTGTATACAGTGATGGTAGCCGTGCAGAACGTCCTGTAACCTGGTCTTC TGTAGAAGTGATTGCTCTTAAATCAGAGCTACCAGTTGTGAAACGTATTGCTCCAAATACTGACTTGAA TTCTGTAGACAAATCTGTTTCCTATGTTTTGATTGATGGAAGTGTTGAAGAGTATGAAGTGGACAAGTG GGAGATTGCCGAAGAAGATAAAGCTAAGTTAGCAATTCCAGGTTCTCGTATTCAAGCGACCGGTTATTT AGAAGGTCAACCAATTCATGCAACCCTTGTGGTAGAAGAAGGCAATCCTGCGGCACCTGCAGTACCAAC TGTAACGGTTGGTGGTGAGGCAGTAACAGGTCTTACTAGTCAAAAACCAATGCAATACCGCACTCTTGC CGCAGCAAACGGCATGCGTGCGAGCATCTTTATTCAGCCTAAAGATGGTGGCCCTCTTCAAACCTATGC AATTCAATTCCTTGAAGAAGCGCCAAAAATTGCTCACTTGAGCTTGCAAGTGGAAAAAAGCTGACAGTCT CAAAGAAGACCAAACTGTCAAATTGTCGGTTCGAGCTCACTATCAAGATGGAACGCAAGCTGTATTACC AGCTGATAAAGTAACCTTCTCTACAAGTGGTGAAGGGGAAGTCGCAATTCGTAAAGGAATGCTTGAGTT GCATAAGCCAGGAGCAGTCACTCTGAACGCTGAATATGAGGGAGCTAAAGACCAAGTTGAACTCACTAT CCAAGCCAATACTGAGAAGAAGATTGCGCAATCCATCCGTCCTGTAAATGTAGTGACAGATTTGCATCA GGAACCAAGTCTTCCAGCAACAGTAACAGTTGAGTATGACAAAGGTTTCCCTAAAAACTCATAAAGTCAC TTGGCAAGCTATTCCGAAAGAAAACTAGACTCCTATCAAACATTTGAAGTACTAGGTAAAGTTGAAGG AATTGACCTTGAAGCGCGTGCAAAAGTCTCTGTAGAAGGTATCGTTTCAGTTGAAGAAGTCAGTGTGAC AACTGGAATGGCAGAAGCACCACAATTACCAGAAAGTGTTCGGACATATGATTCAAATGGTCACGTTTC TGGTCGCTTAGAAGGTACGCAATTAACA

SP052 amino acid (SEQ ID NO:84)

YFGIVDTAGIPKHDFYLYQSQWVSVKKKPMVHLLPHWNWENKELASKVADSEGKIPVRAYSNASSVELF LNGKSLGLKTFNKKQTSDGRTYQEGANANELYLEWKVAYQPGTLEAIARDESGKEIARDKITTAGKPAA VRLIKEDHAIAADGĶDLTYIYYEIVDSQGNVVPTANNLVRFQLHGQGQLVGVDNGEQASRERYKAQADG SWIRKAFNGKGVAIVKSTEQAGKFTLTAHSDLLKSNQVTVFTGKKEGQEKTVLGTEVPKVQTIIGEAPE MPTTVPFVYSDGSRAERPVTWSSVDVSKPGIVTVKGMADGREVEARVEVIALKSELPVVKRIAPNTDLN SVDKSVSYVLIDGSVEEYEVDKWEIAEEDKAKLAIPGSRIQATGYLEGQPIHATLVVEEGNPAAPAVPT VTVGGEAVTGLTSQKPMQYRTLAYGAKLPEVTASAKNAAVTVLQASAANGMRASIFIQPKDGGPLQTYA IQFLEEAPKIAHLSLQVEKADSLKEDQTVKLSVRAHYQDGTQAVLPADKVTFSTSGEGEVAIRKGMLEL HKPGAVTLNAEYEGAKDQVELTIQANTEKKIAQSIRPVNVVTDLHQEPSLPATVTVEYDKGFPKTHKVT WQAIPKEKLDSYQTFEVLGKVEGIDLEARAKVSVEGIVSVEEVSVTTPIAEAPQLPESVRTYDSNGHVS SAKVAWDAIRPEQYAKEGVFTVNGRLEGTQLT

SP053 nucleotide (SEQ ID NO:85)

TCGCTTAGAAGGTACGCAATTAACAACTAAACTTCATGTTCGCGTATCTGCTCAAACTGAGCAAGGTGC $\verb|AAACATTTCTGACCAATGGACCGGTTCAGAATTGCCACTTGCCTTTGCTTCAGACTCAAATCCAAGCGA|$ GAATCGTACTAATCCAGAAGCTTCAGTCGGTGTTCTGTTTGGAGATTCAGGTATCTTGAGCAAACGCTC CGTTGATAATCTAAGTGTCGGATTCCATGAAGACCATGGAGTTGGTGTACCGAAGTCTTATGTGATTGA GTATTATGTTGGTAAGACTGTCCCAACAGCTCCTAAAAACCCTAGTTTTGTTGGTAATGAGGACCATGT CTTTAATGATTCTGCCAACTGGAAACCAGTTACTAATCTAAAAGCCCCTGCTCAACTCAAGGCTGGAGA AATGAACCACTTTAGCTTTGATAAAGTTGAAACCTATGCTGTTCGTATTCGCATGGTTAAAGCAGATAA AACAAGAATCCAAGTTGACGGCAAAGACTTAGCAAACTTCAACCCTGATTTGACAGACTACTACCTTGA GTCTGTAGATGGAAAAGTTCCGGCAGTCACAGCAAGTGTTAGCAACAATGGTCTCGCTACCGTCGTTCC AAGCGTTCGTGAAGGTGAGCCAGTTCGTGTCATCGCGAAAGCTGAAAATGGCGACATCTTAGGAGAATA CCGTCTGCACTTCACTAAGGATAAGAGCTTACTTTCTCATAAACCAGTTGCTGCGGTTAAACAAGCTCG CTTGCTACAAGTAGGTCAAGCACTTGAATTGCCGACTAAGGTTCCAGTTTACTTCACAGGTAAAGACGG CTACGAAACAAAAGACCTGACAGTTGAATGGGAAGAAGTTCCAGCGGAAAATCTGACAAAAGCAGGTCA ATTTACTGTTCGAGGCCGTGTCCTTGGTAGTAACCTTGTTGCTGAGATCACTGTACGAGTGACAAA ACTTGGTGAGACTCTTTCAGATAACCCTAACTATGATGAAAACAGTAACCAGGCCTTTGCTTCAGCAAC CAATGATATTGACAAAAACTCTCATGACCGCGTTGACTATCTCAATGACGGAGATCATTCAGAAAATCG TCGTTGGACAAACTGGTCACCAACACCATCTTCTAATCCAGAAGTATCAGCGGGTGTGATTTTCCGTGA AAATGGTAAGATTGTAGAACGGACTGTTACACAAGGAAAAGTTCAGTTCTTTGCAGATAGTGGTACGGA TGCACCATCTAAACTCGTTTTAGAACGCTATGTCGGTCCAGAGTTTGAAGTGCCAACCTACTATTCAAA CTACCAAGCCTACGACGCAGACCATCCATTCAACAATCCAGAAAATTGGGAAGCTGTTCCTTATCGTGC Table 1 68

SP053 amino acid (SEQ ID NO:86)

AKVAWDAIRPEQYAKEGVFTVNGRLEGTQLTTKLHVRVSAQTEQGANISDQWTGSELPLAFASDSNPSD PVSNVNDKLISYNNQPANRWTNWNRTNPEASVGVLFGDSGILSKRSVDNLSVGFHEDHGVGVPKSYVIE YYVGKTVPTAPKNPSFVGNEDHVFNDSANWKPVTNLKAPAQLKAGEMNHFSFDKVETYAVRIRMVKADN KRGTSITEVQIFAKQVAAAKQGQTRIQVDGKDLANFNPDLTDYYLESVDGKVPAVTASVSNNGLATVVP SVREGEPVRVIAKAENGDILGEYRLHFTKDKSLLSHKPVAAVKQARLLQVGQALELPTKVPVYFTGKDG YETKDLTVEWEEVPAENLTKAGQFTVRGRVLGSNLVAEITVRVTDKLGETLSDNPNYDENSNQAFASAT NDIDKNSHDRVDYLNDGDHSENRRWTNWSPTPSSNPEVSAGVIFRENGKIVERTVTQGKVQFFADSGTD APSKLVLERYVGPEFEVPTYYSNYQAYDADHPFNNPENWEAVPYRADKDIAAGDEINVTFKAIKAKAMR WRMERKADKSGVAMIEMTFLAPSELPQESTQSKILVDGKELADFAENRQDYQITYKGQRPKVSVEENNQ VASTVVDSGEDSFPVLVRLVSESGKQVKEYRIHLTKEKPVSEKTVAAVQEDLPKIEFVEKDLAYKTVEK KDSTLYLGETRVEQEGKVGKERIFTAINPDGSKEEKLREVVEVPTDRIVLVGTKPVAQEAKKPQVSEKA DTKPIDSSEASQTNKAQ

SP054 nucleotide (SEQ ID NO:87)

CTATCACTATGTAAATAAAGAGATTATTTCACAAGAAGCTAAAGATTTAATTCAGACAGGAAAGCCTGACAGGAATGAAGTTGTATATGGTTTTGGTGTATCAAAAAAGATCAGTTGCCTCAAACAGGGACAGAA

SP054 amino acid (SEO ID NO:88)

YHYVNKEIISQEAKDLIQTGKPDRNEVVYGLVYQKDQLPQTGTE

SP055 nucleotide (SEQ ID NO:89)

SP055 amino acid (SEQ ID NO:90)

ETPQSITNQEQARTENQVVETEEAPKEEAPKTEESPKEEPKSEVKPTDDTLPKVEEGKEDSAEPAPVEE VGGEVESKPEEKVAVKPESQPSDKPAEESKVEQAGEPVAPREDEKAPVEPEKQPEAPEEEKAVEETPKQ EESTPDTKAEETVEPKEETVNQSIEQPKVETPAVEKQTEPTEEPKVEQAGEPVAPREDEQAPTAPVEPE KQPEVPEEEKAVEETPKPEDKIKGIGTKEPVDKSELNNQIDKASSVSPTDY

SP056 nucleotide (SEQ ID NO:91)

GGATGCTCAAGAAACTGCGGGAGTTCACTATAAATATGTGGCAGATTCAGAGCTATCATCAGAAGAAAA GAAGCAGCTTGTCTATGATATTCCGACATACGTGGAGAATGATGATGATAACTTATTATCTTGTTTATAA GTTAAATTCTCAAAATCAACTGGCGGAATTGCCAAATACTGGAAGCAAGAATGAGAGGCAA

69

SP056 amino acid (SEQ ID NO:92) DAQETAGVHYKYVADSELSSEEKKQLVYDIPTYVENDDETYYLVYKLNSQNQLAELPNTGSKNERQ

SP057 nucleotide (SEQ ID NO:93)

 $\tt CGACAAAGGTGAGACTGAGGTTCAACCAGAGTCGCCAGATACTGTGGTAAGTGATAAAGGTGAACCAGA$ GCAGGTAGCACCGCTTCCAGAATATAAGGGTAATATTGAGCAAGTAAAACCTGAAACTCCGGTTGAGAA GACCAAAGAACAAGGTCCAGAAAAAACTGAAGAAGTTCCAGTAAAACCAACAGAAGAAACACCAGTAAA TCCAAATGAAGGTACTACAGAAGGAACCTCAATTCAAGAAGCAGAAAATCCAGTTCAACCTGCAGAAGA ATCAACAACGAATTCAGAGAAAGTATCACCAGATACATCTAGCAAAAATACTGGGGAAGTGTCCAGTAA TCCTAGTGATTCGACAACCTCAGTTGGAGAATCAAATAAACCAGAACATAATGACTCTAAAAAATGAAAA TTCAGAAAAACTGTAGAAGAAGTTCCAGTAAATCCAAATGAAGGCACAGTAGAAGGTACCTCAAATCA TACTGGAGAAGTATCCAATAAACCTAGTGATTCAAAACCACCAGTTGAAGAATCAAATCAACCAGAAAA AAACGGAACTGCAACAAAACCAGAAAATTCAGGTAATACAACATCAGAGAATGGACAAACAGAACCAGA ACCATCAAACGGAAATTCAACTGAGGATGTTTCAACCGAATCAAACACATCCAATTCAAATGGAAACGA AGAAATTAAACAAGAAAATGAACTAGACCCTGATAAAAAGGTAGAAGAACCAGAGAAAACACTTGAATT AAGAAAT

SP057 amino acid (SEQ ID NO:94)

DKGETEVQPESPDTVVSDKGEPEQVAPLPEYKGNIEQVKPETPVEKTKEQGPEKTEEVPVKPTEETPVN PNEGTTEGTSIQEAENPVQPAEESTTNSEKVSPDTSSKNTGEVSSNPSDSTTSVGESNKPEHNDSKNEN SEKTVEEVPVNPNEGTVEGTSNQETEKPVQPAEETQTNSGKIANENTGEVSNKPSDSKPPVEESNQPEK NGTATKPENSGNTTSENGQTEPEPSNGNSTEDVSTESNTSNSNGNEEIKQENELDPDKKVEEPEKTLEL

SP058 nucleotide (SEQ ID NO:95)

TAAAGCACCTGCTCAAAGAGTAGATGTAAAAGATATAACTCATTTAACAGATGAAGAAAAAGTTAAGGT AACAATCACATTCCCAGATGGTTCAGTAGTGACGATTCTAGGAAAAGATACAGTTCAACAATCTGCGAA AGGTGAATCTGTAACTCAAGAAGCTACACCAGAGTATAAGCTAGAAAATACACCAGGTGGAGATAAGGG AGGCAATACTGGAAGCTCAGATGCTAATGCGAATGAAGGCGGTGGTAGCCAGGCGGGTGGATCAGCTCA CACAGGTTCACAAAACTCAGCTCAATCACAAGCTTCTAAGCAATTAGCTACTGAAAAAAGAATCAGCTAA AAATGCCATTGAAAAAGCAGCCAAGGACAAGCAGGATGAAATCAAAGGCGCACCGCTTTCTGATAAAGA AAAAGCAGAACTTTTAGCAAGAGTGGAAGCAGAAAAACAAGCAGCTCTCAAAGAGATTGAAAATGCGAA AACTATGGAAGATGTGAAGGAAGCAGAAACGATTGGAGTGCAAGCCATTGCCATGGTTACAGTTCCTAA GAGACCAGTGGCTCCTAAT

SP058 amino acid (SEQ ID NO:96)

NQLVAQDPKAQDSTKLTAEKSTVKAPAQRVDVKDITHLTDEEKVKVAILQANGSALDGATINVAGDGTA TITFPDGSVVTILGKDTVQQSAKGESVTQEATPEYKLENTPGGDKGGNTGSSDANANEGGGSQAGGSAH TGSQNSAQSQASKQLATEKESAKNAIEKAAKDKQDEIKGAPLSDKEKAELLARVEAEKQAALKEIENAK TMEDVKEAETIGVOAIAMVTVPKRPVAPN

SP059 nucleotide (SEQ ID NO:97)

CAAACAGTCAGCTTCAGGAACGATTGAGGTGATTTCACGAGAAAATGGCTCTGGGACACGGGGTGCCTT CACAGAAATCACAGGGATTCTCAAAAAAGACGGTGATAAAAAAATTGACAACACTGCCAAAACAGCTGT GATTCAAAATAGTACAGAAGGTGTTCTCTCAGCAGTTCAAGGGAATGCTAATGCTATCGGCTACATCTC CTTGGGATCTTTAACGAAATCTGTCAAGGCTTTAGAGATTGATGGTGTCAAGGCTAGTCGAGACACAGT TTTAGATGGTGAATACCCTCTTCAACGTCCCTTCAACATTGTTTGGTCTTCTAATCTTTCCAAGCTAGG TCAAGATTTTATCAGCTTTATCCACTCCAAACAAGGTCAACAAGTGGTCACAGATAATAAATTTATTGA AGCTAAAACCGAAACCACGGAATATACAAGCCAACACTTATCAGGCAAGTTGTCTGTTGTAGGTTCCAC TTCAGTATCTTCTTTAATGGAAAAATTAGCAGAAGCTTATAAAAAAAGAAAATCCAGAAGTTACGATTGA TATTACCTCTAATGGGTCTTCAGCAGGTATTACCGCTGTTAAGGAGAAAACCGCTGATATTGGTATGGT TTCTAGGGAATTAACTCCTGAAGAAGGTAAGAGTCTCACCCATGATGCTATTGCTTTAGACGGTATTGC TGTTGTGGTCAATAATGACAATAAGGCAAGCCAAGTCAGTATGGCTGAACTTGCAGACGTTTTTAGTGG CAAATTAACCACCTGGGACAAGATTAAA

SP059 amino acid (SEQ ID NO:98)

KQSASGTIEVISRENGSGTRGAFTEITGILKKDGDKKIDNTAKTAVIQNSTEGVLSAVQGNANAIGYIS LGSLTKSVKALEIDGVKASRDTVLDGEYPLQRPFNIVWSSNLSKLGQDFISFIHSKQGQQVVTDNKFIE AKTETTEYTSQHLSGKLSVVGSTSVSSLMEKLAEAYKKENPEVTIDITSNGSSAGITAVKEKTADIGMV SRELTPEEGKSLTHDAIALDGIAVVVNNDNKASQVSMAELADVFSGKLTTWDKIK

70

SP060 nucleotide (SEQ ID NO:99)

ATTCGATGATGCGGATGAAAAGATGACCCGTGATGAAATTGCCTATATGCTGACAAATAGTGAAGAAAC
ATTGGATGCTGATGAGATTGAGATGCTACAAGGTGTCTTTTCGCTCGATGAACTGATGGCACGAGAGGT
TATGGTTCCTCGAACGGATGCCTTTATGGTGGATATTCAGGATGATAGTCAAGCCATTATCCAAAGTAT
TTTAAAACAAAATTATTCTCGTATCCCGGTTTATGATGGGGATAAGGACAATGTAATTGGAATCATTCA
CACCAAGAGTCTCCTTAAGGCAGGCTTTGTGGACGGTTTTGACAATATTGTTTGGAAGAAATTTTACA
AGATCCACTTTTTGTACCTGAAACTATTTTTGTGGATGACTTGCTAAAAGAACTGCGAAATACCCAAAG

SP060 amino acid (SEQ ID NO:100)

FDDADEKMTRDEIAYMLTNSEETLDADEIEMLQGVFSLDELMAREVMVPRTDAFMVDIQDDSQAIIQSI LKQNYSRIPVYDGDKDNVIGIIHTKSLLKAGFVDGFDNIVWKRILQDPLFVPETIFVDDLLKELRNTQR OM

SP062 nucleotide (SEQ ID NO:101)

SP062 amino acid (SEQ ID NO:102)

ESRSKVDEAVSKFEKDSSSSSSSSSSSTKPEASDTAKPNKPTEPGEKVAEAKKKVEEAEKKAKDQKEEDR RNYPTITYKTLELEIAESDVEVKKAELELVKVKANEPRDEQ

SP063 nucleotide (SEQ ID NO:103)

ATGGACAACAGGAAACTGGGACGAGGTTATATCTGGTAAGATTGACAAGTACAAAGATCCAGATATTCC
AACAGTTGAATCACAAGAAGTTACGTCAGACTCTAGTGATAAAGAAATAACGGTAAGGTATGACCGTTT
ATCAACACCAGAAAAAACCAATCCCACAACCAAATCCAGAGCATCCAAGTGTTCCGACACCAAACCCAGA
ACTACCAAATCAAGAGACTCCAACACCAGATAAACCAACTCCAGAACCAGGTACTCCAAAAACTGAAAC
TCCAGTGAATCCAGACCCAGAAGTTCCGACTTATGAGACAGGTAAGAGAGGAATTGCCAAAACACAGG
TACAGAAGCTAAT

SP063 amino acid (SEQ ID NO:104)

WTTGNWDEVISGKIDKYKDPDIPTVESQEVTSDSSDKEITVRYDRLSTPEKPIPQPNPEHPSVPTPNPE LPNQETPTPDKPTPEPGTPKTETPVNPDPEVPTYETGKREELPNTGTEAN

SP064 nucleotide (SEQ ID NO:105)

Table 1

CGGCGACGCTAAAAACCCAGCCCTATCTCCACTAGGCGAAAACGTGAAGACCAAAGGTCAATACTTCTA
TCAANTAGCCTTGGACGGAAATGTAGCTGGCAAAGAAAAACAAGCGCTCATTGACCAGTTCCGAGCAAA
NGGTACTCAAACTTACAGCGCTACAGTCAATGTCTATGGTAACAAAGACGGTAAACCAGACTTGGACAA
CATCGTAGCAACCTAAAAAAGTCACTATTAACATAAACGGTTTAATTTCTAAAGAAACAGTTCAAAAAGC
CGTTGCAGACAACGTTAANGACAGTATCGATGTTCCAGCAGCCTACCTAGAAAAAAGCCAAGGGTGAAGG
TCCATTCACAGCAGGTGTCAACCATGTGATTCCATACGAACTCTTCGCAGGTGATGGTATGTTGACTCG
TCTCTTGCTCAAGGCATCTGACAAGGCACCATGGTCAGATAACGGNGACGCTAAAAAACCCAGCNCTATC
TCCACTAGGTGAAAACGTGAAGACCAAAGGTCAATACTTCTATCAANTAGCCTTGGACGGAAATGTAGC
TGGCAAAGAAAAACAAGCGCTCATTGACCAGTTCCGAGCAAACGGTACTCAAACTTACAGCGCTACAGT
CAATGTCTATGGTAACAAAGACGGTAAACCAGGACTTGGACAACATCGTAGCAACTAAAAAAAGTCACTAT
TAAGATAAATGTTAAAGAAACATCAGACACAGCAAATGGTTCATTATCACCTTCTAACTCTGGTTCTGG
CGTGACTCCGATGAATCACAATCATGCTACAGGTACTACAGATAGCATGCTTGACACCATGACAAG
TTCTACCAACACGATGGCAGGTGAAAACATGGCTGCTTCTGACACGATGACAAG
AGAGGATAAAGCTATG

SP064 amino acid (SEQ ID NO:106)

DGLNPTPGQVLPEETSGTKEGDLSEKPGDTVLTQAKPEGVTGNTNSLPTPTERTEVSEETSPSSLDTLF
EKDEEAQKNPELTDVLKETVDTADVDGTQASPAETTPEQVKGGVKENTKDSIDVPAAYLEKAEGKGPFT
AGVNQVIPYELFAGDGMLTRLLLKASDNAPWSDNGTAKNPALPPLEGLTKGKYFYEVDLNGNTVGKQGQ
ALIDQLRANGTQTYKATVKVYGNKDGKADLTNLVATKNVDININGLVAKETVQKAVADNVKDSIDVPAA
YLEKAKGEGPFTAGVNHVIPYELFAGDGMLTRLLLKASDKAPWSDNGDAKNPALSPLGENVKTKGQYFY
QXALDGNVAGKEKQALIDQFRAXGTQTYSATVNVYGNKDGKPDLDNIVATKKVTININGLISKETVQKA
VADNVXDSIDVPAAYLEKAKGEGPFTAGVNHVIPYELFAGDGMLTRLLLKASDKAPWSDNGDAKNPALS
PLGENVKTKGQYFYQXALDGNVAGKEKQALIDQFRANGTQTYSATVNVYGNKDGKPDLDNIVATKKVTI
KINVKETSDTANGSLSPSNSGSGVTPMNHNHATGTTDSMPADTMTSSTNTMAGENMAASANKMSDTMMS
EDKAM

SP065 nucleotide (SEQ ID NO:107)

TTCCAATCAAAAACAGGCAGATGGTAAACTCAATATCGTGACAACCTTTTACCCTGTCTATGArTTTAC
CAAGCAAGTCGCAGGAGATACGGCTAATGTAGAACTCCTAATCGGTGCTGGGACAGAACCTCATGAATA
CGAACCATCTGCCAAGGCAGTTGCCAAAATCCAAGATGCAGATACCTTCGTTTATGAAAATGAAAACAT
GGAAACATGGGTACCTAAATTGCTAGATACCTTGGATAAGAAAAAAGTGAAAACCATCAAGGCGACAGG
CGATATGTTGCTCTTGCCAGGTGGCGAGGAAGAAGAGGGGAGACCATGACCATGGAGAAGAAGATCATCA
CCATGAGTTTGACCCCCATGTTTGGTTATCACCAGTTCGTGCCATLAAACTAGTAGAGCACCATCCGCG
ACACTTGTCAGCAGATTATCCTGATAAAAAAGAGACCTTTGAGAAGAATGCAGCTGCCTATATCGAAAA
ATTGCAAGCCTTGGATAAGGCTTACGCAGAAGGTTTGTCTCAAGCAAAACAAAAGAGCTTTGTGACTCA
ACACGCAGCCTTTAACTATCTTGCCTTGGACTATGGGACTC

SP065 amino acid (SEQ ID NO:108)

 ${\tt SNQKQADGKLNIVTTFYPVYEFTKQVAGDTANVELLIGAGTEPHEYEPSAKAVAKIQDADTFVYENENM}\\ {\tt ETWVPKLLDTLDKKKVKTIKATGDMLLLPGGEEEEGDHDHGEEGHHHEFDPHVWLSPVRAIKLVEHHPR\\ {\tt HLSADYPDKKETFEKNAAAYIEKLQALDKAYAEGLSQAKQKSFVTQHAAFNYLALDYGT}\\$

SP067 nucleotide (SEQ ID NO:109)

 $AGGAGATGTGGTTCTTCTTAGTCCTGCCA \dot{A}TGCTAGCTGGGATATGTATGCTAACTTTGAAGTACGTGGCGGACCTCTTTATCGACACAGTAGCGGAGTTAAAAGAA$

72

SP067 amino acid (SEQ ID NO:110)

GITGSNGKTTTTTMIGEVLTAAGQHGLLSGNIGYPASQVAQIASDKDTLVMELSSFQLMGVQEFHPEIA VITNLMPTHIDYHGSFSEYVAAKWNIQNKMTAADFLVLNFNQDLAKDLTSKTEATVVPFSTLEKVDGAY LEDGQLYFRGEVVMAANEIGVPGSHNVENALATIAVAKLRDVDNQTIKETLSAFGGVKHRLQFVDDIKG VKFYNDSKSTNILATQKALSGFDNSKVVLIAGGLDRGNEFDELVPDITGLKKMVILGQSAERVKRAADK AGVAYVEATDIADATRKAYELATQGDVVLLSPANASWDMYANFEVRGDLFIDTVAELKE

SP068 nucleotide (SEQ ID NO:111)

AAGTTCATCGAAGATGGTTGGGAAGTCCACTATATCGGGGACAAGTGTGGTATCGAACACCAAGAAATC
CTTAAGTCAGGTTTGGATGTCACCTTCCATTCTATTGCGACTGGAAAATTGCGTCGCTATTTCTCTTGG
CAAAATATGCTGGACGTCTTCAAAGTTGGTTGGGGAATTGTCCAATCGCTCTTTATCATGTTGCGACTG
CGTCCACAGACCCTTTTTTCAAAAGGGGGGGCTTTGTCTCAGTACCGCCTGTTATCGCTGCGGTGTCCA
GGAGTGCCTGTCTTTATTCACGAATCTGACCTGTCTATGGGCTTGGCCAATAAAATCGCCTATAAATTT
GCGACTAAGATGTATTCAACCTTTGAACAAGCTTCGAGTTTGGCTAAGGTTGAGCATGTGGGAGCGG

SP068 amino acid (SEQ ID NO:112)

SSSKMVGKSTISGTSVVSNTKKSLSQVWMSPSILLRLENCVAISLGKICWTSSKLVGELSNRSLSCCDC VHRPFFQRGALSQYRLLSLRVCQECLSLFTNLTCLWAWPIKSPINLRLRCIQPLNKLRVWLRLSMWER

SP069 nucleotide (SEQ ID NO:113)

ATCGCTAGCTAGTGAAATGCAAGAAAGTACACGTAAATTCAAGGTTACTGCTGACCTAACAGATGCCGG
TGTTGGAACGATTGAAGTTCCTTTGAGCATTGAAGATTTACCCAATGGGCTGACCGTGTGGCGACTCC
GCAAAAAATTACAGTCAAGATTGGTAAGAAGGCTCAGAAGGATAAGGTAAAGATTGTACCAGAGATTGA
CCCTAGTCAAATTGATAGTCGGGTACAAATTGAAAATGTCATGGTGTCAGATAAAGAAGTGTCTATTAC
GAGTGACCAAGAGACATTGGATAGAATTGATAAGATTATCGCTGTTTTTGCCAACTAGCGAACGTATAAC
AGGTAATTACAGTGGTTCAGTACCTTTGCAGGCAATCGACCGCAATGGTGTTCTTACCGGCAGTTAT
CACTCCGTTTGATACAATAATGAAGGTGACTACAAAACCAGTAGCACCAAGTTCAAGCACATCAAATTC
AAGTACAAGCAGTTCATCGGAGACATCTTCGTCAACGAAAGCAACTAGTTCAAAAACGAAT

SP069 amino acid (SEQ ID NO:114)

SLASEMQESTRKFKVTADLTDAGVGTIEVPLSIEDLPNGLTAVATPQKITVKIGKKAQKDKVKIVPEID PSQIDSRVQIENVMVSDKEVSITSDQETLDRIDKIIAVLPTSERITGNYSGSVPLQAIDRNGVVLPAVI TPFDTIMKVTTKPVAPSSSTSNSSTSSSSETSSSTKATSSKTN

SP070 nucleotide (SEQ ID NO:115)

GCACCAGATGGGGCACAAGGTTCAGGGATCAGATGTTGAAAAGTACTACTTTACCCAACGCGGTCTTGA GCAGGCAGGAATTACCATTCTTCCTTTTGATGAAAAAAATCTAGACGGTGATATGGAAATTATCGCTGG AAATGCCTTTCGTCCAGATAACAACGTCGAAATTGCCTATGCGGACCAAAATGGTATCAGCTACAAACG TTACCATGAGTTTCTAGGTAGCTTTATGCGTGACTTTGTTAGCATGGGAGTAGCAGGAGCACATGGAAA AACTTCAACGACAGGTATGTTGTCTCATGTCTTGTCTCACATTACAGATACCAGCTTCTTGATTGGAGA ${\tt TGGGACAGGTCGTGGTTCGGCCAATGCCAAATATTTTGTCTTTGAATCTGACGAATATGAGCGTCACTT}$ CATGCCTTACCACCCAGAATACTCTATTATCACCAACATTGACTTTGACCATCCAGATTATTTCACAAG TCTCGAGGATGTTTTTAATGCCTTTAACGACTATGCCAAACAATCACCAAGGGTCTTTTTGTCTATGG TGAAGATGCTGAATTGCGTAAGATTACGTCTGATGCACCAATTTATTATTATGGTTTTGAAGCTGAAGG CAATGACTTTGTAGCTAGTGATCTTCTTCGTTCAATAACTGGTTCAACCTTCACCGTTCATTCCGTGG ACAAAACTTGGGGCAATTCCACATTCCAACCTTTGGTCGTCACAATATCATGAATGCGACAGCCGTTAT TGGTCTTCTTTACACAGCAGGATTTGATTTGAACTTGGTGCGTGAGCACTTGAAAACATTTGCCGGTGT TAAACGTCGTTTCACTGAGAAAATTGTCAATGATACAGTGATTATCGATGACTTTGCCCACCATCCAAC ACCGCATACCTTTACAAGAACCATTGCCTTGTTGGACGACTTTGCCCATGCTTTAAACCAAGCAGATGC $\tt TGTTTATCTAGCGCAAATTTATGGCTCGGCTCGTGAAGTAGATCATGGTGACGTTAAGGTAGAAGACCT$ AGCCAACAAAATCAACAAAAAACACCAAGTGATTACTGTTGAAAATGTTTCTCCACTCCTAGACCATGA CAATGCTGTTTACGTCTTTATGGGAGCAGGAGACATCCAAACCTATGAATACTCATTTGAGCGTCTCTT GTCTAACTTGACAAGCAATGTTCAA

SP070 amino acid (SEQ ID NO:116)

HQMGHKVQGSDVEKYYFTQRGLEQAGITILPFDEKNLDGDMEIIAGNAFRPDNNVEIAYADQNGISYKR YHEFLGSFMRDFVSMGVAGAHGKTSTTGMLSHVLSHITDTSFLIGDGTGRGSANAKYFVFESDEYERHF MPYHPEYSIITNIDFDHPDYFTSLEDVFNAFNDYAKQITKGLFVYGEDAELRKITSDAPIYYYGFEAEG NDFVASDLLRSITGSTFTVHFRGQNLGQFHIPTFGRHNIMNATAVIGLLYTAGFDLNLVREHLKTFAGV KRRFTEKIVNDTVIIDDFAHHPTEIIATLDAARQKYPSKEIVAVFQPHTFTRTIALLDDFAHALNQADA VYLAQIYGSAREVDHGDVKVEDLANKINKKHQVITVENVSPLLDHDNAVYVFMGAGDIQTYEYSFERLL SNLTSNVQ

SP071 nucleotide (SEQ ID NO:117)

TTTTAACCCAACTGTTGGTACTTTCCTTTTTACTGCAGGATTGAGCTTGTTAGTTTTATTGGTTTCTAA AAGGGAAAATGGAAAGAAACGACTTGTTCATTTTCTGCTGTTGACTAGCATGGGAGTTCAATTGTTGCC GGCCAGTGCTTTTGGGTTGACCAGCCAGATTTTATCTGCCTATAATAGTCAGCTTTCTATCGGAGTCGG GGAACATTTACCAGAGCCTCTGAAAATCGAAGGTTATCAATATATTGGTTATATCAAAACTAAGAAACA GGATAATACAGAGCTTTCAAGGACAGTTGATGGGAAATACTCTGCTCAAAGAGATAGTCAACCAAACTC TACAAAAACATCAGATGTAGTTCATTCAGCTGATTTAGAATGGAACCAAGGACAGGGGAAGGTTAGTTT TAATGATTCATTCGCAAGTCAAGTTGAGCAGAATCCGGATCACAAAGGAGAATCTGTAGTTCGACCAAC AGTGCCAGAACAAGGAAATCCTGTGTCTGCTACAACGGTGCAGAGTGCGGAAGAGGAAGTATTGGCGAC GACAAATGATCGACCAGAGTATAAACTTCCATTGGAAACCAAAGGCACGCAAGAACCCGGTCATGAGGG TGAAGCCGCAGTCCGTGAAGACTTACCAGTCTACACTAAGCCACTAGAAACCAAAGGTACACAAGGACC CGGACATGAAGGTGAAGCTGCAGTTCGCGAGGAAGAACCAGCTTACACAGAACCGTTAGCAACGAAAGG CACGCAAGAGCCAGGTCATGAGGGCAAAGCTACAGTCCGCGAAGAGACTCTAGAGTACACGGAACCGGT AGCGACAAAAGGCACACAAGAACCCGAACATGAGGGCGAaCGGsCAGTAGAAGAAGAACTTCCGGCTTT AGAGGTCACTACACGAAATAGAACGGAAATCCAGAATATTCCTTATACAACAGAAGAAATTCAGGATCC AACACTTCTGAAAAATCGTCGTAAGATTGAACGACAAGGGCAAGCAGGGACACGTACAATTCAATATGA AGACTACATCGTAAATGGTAATGTCGTAGAAACTAAAGAAGTGTCACGAACTGAAGTAGCTCCGGTCAA CGAAGTCGTTAAAGTAGGAACACTTGTGAAAGTTAAACCTACAGTAGAAATTACAAACTTAACAAAAGT TGAGAACAAAAATCTATAACTGTAAGTTATAACTTAATAGACACTACCTCAGCATATGTTTCTGCAAA AACGCAAGTTTTCCATGGAGACAAGCTAGTTAAAGAGGTGGATATAGAAAATCCTGCCAAAGAGCAAGT AATATCAGGTTTAGATTACTACACACCGTATACAGTTAAAACACACCTAACTTATAATTTGGGTGAAAA TAATGAGGAAAATACTGAAACATCAACTCAAGATTTCCAATTAGAGTATAAGAAAATAGAGATTAAAGA TATTGATTCAGTAGAATTATACGGTAAAGAAAATGATCGTTATCGTAGATATTTAAGTCTAAGTGAAGC AAAATCTATTACAGAAAATACGGATGGAACGTATAAAGTGACGGTAGCCGTTGATCAACTTGTCGAAGA AGGTACAGACGGTTACAAAGATGATTACACATTTACTGTAGCTAAATCTAAAGCAGAGCAACCAGGAGT AGATATGACCGCAGATGAGGTGAGCTTAGGCGATAAGCAGACAAGTTATCTCACAGGTGCATTTACAGG GAGCTTGATCGGTTCTGATGGAACAAAATCGTATGCCATTTATGATTTGAAGAAACCATTATTTGATAC ATTAAATGGTGCTACAGTTAGAGATTTGGATATTAAAACTGTTTCTGCTGATAGTAAAGAAAATGTCGC AGCGCTGGCGAAGGCAGCGAATAGCGCGAATATTAATAATGTTGCAGTAGAAGGAAAAATCTCAGGTGC GAAATCTGTTGCGGGATTAGTAGCGAGCGCAACAAATACAGTGATAGAAAACAGCTCGTTTACAGGGAA ACTTATCGCAAATCACCAGGACAGTAATAAAAATGATACTGGAGGAATAGTAGGTAATATAACAGGAAA TAGTTCGAGAGTTAATAAAGTTAGGGTAGATGCCTTAATCTCTACTAATGCACGCAATAATAACCAAAC AGCTGGAGGGATAGTAGGTAGATTAGAAAATGGTGCATTGATATCTAATTCGGTTGCTACTGGAGAAAT ACGAAATGGTCAAGGATATTCTAGAGTCGGAGGAATAGTAGGATCTACGTGGCAAAACGGTCGAGTAAA TAATGTTGTGAGTAACGTAGATGTTGGAGATGGTTATGTTATCACCGGTGATCAATACGCAGCAGCAGA CCAAATAGACGCGAAAGTTGCTGATTATGGAATCACAGTAACTCTTGATGATACTGGGCAAGATTTAAA CAACATAGAAAAACTGATGCCATTCTACAATAAAGACCTAGTAGTTCACTATGGTAACAAAGTAGCGAC AACAGATAAACTTTACACTACAGAATTGTTAGATGTTGTGCCGATGAAAGATGATGAAGTAGTAACGGA TATTAATAAGAAAAATTCAATAAATAAAGTTATGTTACATTCAAAGATAATACAGTAGAATACCT AGATGTAACATTCAAAGAAAACTTCATAAACAGTCAAGTAATCGAATACAATGTTACAGGAAAAGAATA TATATTCACACCAGAAGCATTTGTTTCAGACTATACAGCGATAACGAATAACGTACTAAGCGACTTGCA AAATGTAACACTTAAC

NVTLN

FNPTVGTFLFTAGLSLLVLLVSKRENGKKRLVHFLLLTSMGVQLLPASAFGLTSQILSAYNSQLSIGVG
EHLPEPLKIEGYQYIGYIKTKKQDNTELSRTVDGKYSAQRDSQPNSTKTSDVVHSADLEWNQGQGKVSL
QGEASGDDGLSEKSSIAADNLSSNDSFASQVEQNPDHKGESVVRPTVPEQGNPVSATTVQSAEEVLAT
TNDRPEYKLPLETKGTQEPGHEGEAAVREDLPVYTKPLETKGTQGPGHEGEAAVREEEPAYTEPLATKG
TQEPGHEGKATVREETLEYTEPVATKGTQEPEHEGERXVEEELPALEVTTRNRTEIQNIPYTTEEIQDP
TLLKNRRKIERQGQAGTRTIQYEDYIVNGNVVETKEVSRTEVAPVNEVVKVGTLVKVKPTVEITNLTKV
ENKKSITVSYNLIDTTSAYVSAKTQVFHGDKLVKEVDIENPAKEQVISGLDYYTPYTVKTHLTYNLGEN
NEENTETSTQDFQLEYKKIEIKDIDSVELYGKENDRYRRYLSLSEAPTDTAKYFVKVKSDRFKEMYLPV
KSITENTDGTYKVTVAVDQLVEEGTDGYKDDYTFTVAKSKAEQPGVYTSFKQLVTAMQSNLSGVYTLAS
DMTADEVSLGDKQTSYLTGAFTGSLIGSDGTKSYAIYDLKKPLFDTLNGATVRDLDIKTVSADSKENVA
ALAKAANSANINNVAVEGKISGAKSVAGLVASATNTVIENSSFTGKLIANHQDSNKNDTGGIVGNITGN
SSRVNKVRVDALISTNARNNNQTAGGIVGRLENGALISNSVATGEIRNGQGYSRVGGIVGSTWQNGRVN
NVVSNVDVGDGGYVITGDQYAAADVKNASTSVDNRKADRFATKLSKDQIDAKVADYGITVTLDDTGQDLK
RNLREVDYTRLNKAEAERKVAYSNIEKLMPFYNKDLVVHYGNKVATTDKLYTTELLDVVPMKDDEVVTD
INNKKNSINKVMLHFKDNTVEYLDVTFKENFINSQVIEYNVTGKEYIFTPEAFVSDYTAITNNVLSDLQ

74

SP072 nucleotide (SEQ ID NO:119)

TTTTAACCCAACTGTTGGTACTTTCCTTTTTACTGCAGGATTGAGCTTGTTAGTTTTATTGGTTTCTAA AAGGGAAAATGGAAAGAAACGACTTGTTCATTTTCTGCTGTTGACTAGCATGGGAGTTCAATTGTTGCC GGCCAGTGCTTTTGGGTTGACCAGCCAGATTTTATCTGCCTATAATAGTCAGCTTTCTATCGGAGTCGG GGAACATTTACCAGAGCCTCTGAAAATCGAAGGTTATCAATATTTGGTTATATCAAAACTAAGAAACA GGATAATACAGAGCTTTCAAGGACAGTTGATGGGAAATACTCTGCTCAAAGAGATAGTCAACCAAACTC TACAAAAACATCAGATGTAGTTCATTCAGCTGATTTAGAATGGAACCAAGGACAGGGGAAGGTTAGTTT TAATGATTCATTCGCAAGTCAAGTTGAGCAGAATCCGGATCACAAAGGAGAATCTGTAGTTCGACCAAC AGTGCCAGAACAAGGAAATCCTGTGTCTGCTACAACGGTGCAGAGTGCGGAAGAGGAAGTATTGGCGAC GACAAATGATCGACCAGAGTATAAACTTCCATTGGAAACCAAAGGCACGCAAGAACCCGGTCATGAGGG TGAAGCCGCAGTCCGTGAAGACTTACCAGTCTACACTAAGCCACTAGAAACCAAAGGTACACAAGGACC CGGACATGAAGGTGAAGCTGCAGTTCGCGAGGAAGAACCAGCTTACACAGAACCGTTAGCAACGAAAGG CACGCAAGAGCCAGGTCATGAGGGCAAAGCTACAGTCCGCGAAGAGACTCTAGAGTACACGGAACCGGT AGCGACAAAAGGCACACAAGAACCCGAACATGAGGGCGGACGGSCAGTAGAAGAAGAACTTCCGGCTTT AGAGGTCACTACACGAAATAGAACGGAAATCCAGAATATTCCTTATACAACAGAAGAAATTCAGGATCC AACACTTCTGAAAAATCGTCGTAAGATTGAACGACAAGGGCAAGCAGGGACACGTACAATTCAATATGA AGACTACATCGTAAATGGTAATGTCGTAGAAACTAAAGAAGTGTCACGAACTGAAGTAGCTCCGGTCAA CGAAGTCGTTAAAGTAGGAACACTTGTGAAAGTTAAACCTACAGTAGAAATTACAAACTTAACAAAAGT TGAGAACAAÅAAATCTATAACTGTAAGTTATAACTTAATAGACACTACCTCAGCATATGTTTCTGCAAA AACGCAAGTTTTCCATGGAGACAAGCTAGTTAAAGAGGTGGATATAGAAAATCCTGCCAAAGAGCAAGT AATATCAGGTTTAGATTACTACACACCGTATACAGTTAAAACACACCTAACTTATAATTTGGGTGAAAA TAATGAGGAAAATACTGAAACATCAACTCAAGATTTCCAATTAGAGTATAAGAAAATAGAGATTAAAGA TATTGATTCAGTAGAATTATACGGTAAAGAAAATGATCGTTATCGTAGA

SP072 amino acid (SEQ ID NO:120)

FNPTVGTFLFTAGLSLLVLLVSKRENGKKRLVHFLLLTSMGVQLLPASAFGLTSQILSAYNSQLSIGVG EHLPEPLKIEGYQYIGYIKTKKQDNTELSRTVDGKYSAQRDSQPNSTKTSDVVHSADLEWNQGQGKVSL QGEASGDDGLSEKSSIAADNLSSNDSFASQVEQNPDHKGESVVRPTVPEQGNPVSATTVQSAEEEVLAT TNDRPEYKLPLETKGTQEPGHEGEAAVREDLPVYTKPLETKGTQGPGHEGEAAVREEEPAYTEPLATKG TQEPGHEGKATVREETLEYTEPVATKGTQEPEHEGERXVEEELPALEVTTRNRTEIQNIPYTTEEIQDP TLLKNRRKIERQGQAGTRTIQYEDYIVNGNVVETKEVSRTEVAPVNEVVKVGTLVKVKPTVEITNLTKV ENKKSITVSYNLIDTTSAYVSAKTQVFHGDKLVKEVDIENPAKEQVISGLDYYTPYTVKTHLTYNLGEN NEENTETSTODFOLEYKKIEIKDIDSVELYGKENDRYRR

SP073 nucleotide (SEQ ID NO:121)

TCGTAGATATTTAAGTCTAAGTGAAGCGCCGACTGATACGGCTAAATACTTTGTAAAAGTGAAATCAGA
TCGCTTCAAAGAAATGTACCTACCTGTAAAATCTATTACAGAAAATACGGATGGAACGTATAAAGTGAC
GGTAGCCGTTGATCAACTTGTCGAAGAAGGTACAGACGGTTACAAAGATGATTACACATTTACTGTAGC
TAAATCTAAAGCAGAGCAACCAGGAGTTTACACATCCTTTAAACAGCTGGTAACAGCCATGCAAAGCAA
TCTGTCTGGTGTCTATACATTGGCTTCAGATATGACCGCAGATGAGGTGAGCTTAGGCGATAAGCAGAC

75

AAGTTATCTCACAGGTGCATTTACAGGGAGCTTGATCGGTTCTGATGGAACAAAATCGTATGCCATTTA TGATTTGAAGAAACCATTATTTGATACATTAAATGGTGCTACAGTTAGAGATTTGGATATTAAAACTGT TTCTGCTGATAGTAAAGAAAATGTCGCAGCGCTGGCGAAGGCAGCGAATAGCGCGAATATTAATAATGT GATAGAAAACAGCTCGTTTACAGGGAAACTTATCGCAAATCACCAGGACAGTAATAAAAATGATACTGG AGGAATAGTAGGTAATATAACAGGAAATAGTTCGAGAGTTAATAAAGTTAGGGTAGATGCCTTAATCTC ATCTAATTCGGTTGCTACTGGAGAAATACGAAATGGTCAAGGATATTCTAGAGTCGGAGGAATAGTAGG ATCTACGTGGCAAAACGGTCGAGTAAATAATGTTGTGAGTAACGTAGATGTTGGAGATGGTTATGTTAT CACCGGTGATCAATACGCAGCAGCAGATGTGAAAAATGCAAGTACATCAGTTGATAATAGAAAAGCAGA CAGATTCGCTACAAAATTATCAAAAGACCAAATAGACGCGAAAGTTGCTGATTATGGAATCACAGTAAC AGAAGCTGAAAGAAAAGTAGCTTATAGCAACATAGAAAAACTGATGCCATTCTACAATAAAGACCTAGT AGTTCACTATGGTAACAAAGTAGCGACAACAGATAAACTTTACACTACAGAATTGTTAGATGTTGTGCC TTTCAAAGATAATACAGTAGAATACCTAGATGTAACATTCAAAGAAAACTTCATAAACAGTCAAGTAAT CGAATACAATGTTACAGGAAAAGAATATATATTCACACCAGAAGCATTTGTTTCAGACTATACAGCGAT AACGAATAACGTACTAAGCGACTTGCAAAATGTAACACTTAAC

SP073 amino acid (SEQ ID NO:122)

RRYLSLSEAPTDTAKYFVKVKSDRFKEMYLPVKSITENTDGTYKVTVAVDQLVEEGTDGYKDDYTFTVA
KSKAEQPGVYTSFKQLVTAMQSNLSGVYTLASDMTADEVSLGDKQTSYLTGAFTGSLIGSDGTKSYAIY
DLKKPLFDTLNGATVRDLDIKTVSADSKENVAALAKAANSANINNVAVEGKISGAKSVAGLVASATNTV
IENSSFTGKLIANHQDSNKNDTGGIVGNITGNSSRVNKVRVDALISTNARNNNQTAGGIVGRLENGALI
SNSVATGEIRNGQGYSRVGGIVGSTWQNGRVNNVVSNVDVGDGYVITGDQYAAADVKNASTSVDNRKAD
RFATKLSKDQIDAKVADYGITVTLDDTGQDLKRNLREVDYTRLNKAEAERKVAYSNIEKLMPFYNKDLV
VHYGNKVATTDKLYTTELLDVVPMKDDEVVTDINNKKNSINKVMLHFKDNTVEYLDVTFKENFINSQVI
EYNVTGKEYIFTPEAFVSDYTAITNNVLSDLQNVTLN

SP074 nucleotide (SEQ ID NO:123)

SP074 amino acid (SEQ ID NO:124)

FGFEGSKRGQFAVEGINQLREHVDTLLIISNNNLLEIVDKKTPLLEALSEADNVLRQGVQGITDLITNP GLINLDFADVKTVMANKGNALMGIGIGSGEERVVEAARKAIYSPLLETTIDGAEDVIVNVTGGLDLTLI EAEEASQIVNQAAGQGVNIWLGTSIDESMRDEIRVTVVATGVRQDRVEKVVAPQARSATNYRETVKPAH SHGFDRHFDMAETVELPKQNPRRLEPTQASAFGDWDLRRESIVRTTDSVVSPVERFEAPISQDEDELDT PPFFKNR

SP075 nucleotide (SEQ ID NO:125)

CTACTACCTCTCGAGAGAAAGTGACCTAGAGGTGACCGTTTTTGACCATGAGCAAGGTCAAGCCACCAAGGCCACCAAGGCCAGCAGGAAATTATCAGTCCTTGGTTTTCCAAACGCCGTAATAAAGCCTGGTACAAGATGGCGCGCTTTGGGGGGCTGATTTTATGTGGATTTATTAGCTGATTTAGAGAAATCAGGACAAGAAATCGACTTTTACCAGCGTTCGGGAGTCTTTCTCTTGAAAAAGGATGAATCCAATTTGGAAGAACTTTATCAACTGGCCCTCCAGCGCAGAGAAATCTCCCTTGATAGGGCAATTAGCCATTCTGAACCAAGCCTCAGCTAATGAATTATCCCTGGTTTGCAGGGGATTTGACCGCCTGCTCTATGCTTCTGGTGGAGCGAGAGTAGATGGCCAACT

GCTTGCCCAAGACATGGAAGATTACCCTGTTGTCATGCCAGAAGGGGAGTGGGATTTGATTCCCTTTGC AGGTGGGAAATTATCCTTAGGCGCTACCCACGAAAATGACATGGGATTTGATTTGACGGTAGATGAAAC CTTGCTCCAACAAATGGAGGGGCCACCTTGACTCACTATCTGATTTTGGCTGAAGCTACTTCAAAATC TGAGCGTGTTGGAATCCGTGCCTACACCAGTGATTTCTCTCTTTTGGGCAGGTGCCTGACTTAAC TGGTGTCTATGCAGCCAGTGGACTAGGTTCATCAGGCCTCACAACTGGTCCTATCATTGGTTACCATCT AGCCCAACTGATCCAAGACAAGGAGTTGACCTTGGACCCTCTAAATTACCCAATTGAAAACTATGTCAA ACGAGTAAAAAAGCGAA

SP075 amino acid (SEQ ID NO:126)

YYLSRESDLEVTVFDHEQGQATKAAAGIISPWFSKRRNKAWYKMARLGADFYVDLLADLEKSGQEIDFY QRSGVFLLKKDESNLEELYQLALQRREESPLIGQLAILNQASANELFPGLQGFDRLLYASGGARVDGQL LVTRLLEVSHVKLVKEKVTLTPLASGYQIGEEEFEQVILATGAWLGDMLEPLGYEVDVRPQKGQLRDYQ LAQDMEDYPVVMPEGEWDLIPFAGGKLSLGATHENDMGFDLTVDETLLQQMEEATLTHYLILAEATSKS ERVGIRAYTSDFSPFFGQVPDLTGVYAASGLGSSGLTTGPIIGYHLAQLIQDKELTLDPLNYPIENYVK RVKSE

SP076 nucleotide (SEQ ID NO:127)

TAAGGTCAAAAGTCAGACCGCTAAGAAAGTGCTAGAAAAGATTGGAGCTGACTCGGTTATCTCGCCAGA GTATGAAATGGGGCAGTCTCTAGCACAGACCATTCTTTTCCATAATAGTGTTGATGTCTTTCAGTTGGA TAAAAATGTGTCTATCGTGGAGATGAAAATTCCTCAGTCTTGGGCAGGTCAAAGTCTGAGTAAATTAGA CCTCCGTGGCAAATACAATCTGAATATTTTGGGTTTCCGAGAGCAGGAAAATTCCCCATTGGATGTTGA ATTTGGACCAGATGACCTCTTGAAAGCAGATACCTATATTTTGGCAGTCATCAACAACCAGTATTTGGA TACCCTA

SP076 amino acid (SEQ ID NO:128)

KVKSQTAKKVLEKIGADSVISPEYEMGQSLAQTILFHNSVDVFQLDKNVSIVEMKIPQSWAGQSLSKLD LRGKYNLNILGFREQENSPLDVEFGPDDLLKADTYILAVINNQYLDTL

SP077 nucleotide (SEQ ID NO:129)

SP077 amino acid (SEQ ID NO:130)

DGSQDQTQEIAECLASKYPNIVRAIYQENKCHGGAVNRGLVEASGRYFKVVDSDDWVDPRAYLKILETC

SP078 nucleotide (SEQ ID NO:131)

TAGAGGCTTTGCCAAATGGTGGGAAGGGCACGAGCGTCGAAAAGAGGGAACGCTTTGTCAAACAAGAAGA AAAAGCTCGCCAAAAGGCTGAGAAAGAGGCTAGATTAGAACAAGAAGAGACTGAAAAAAGCCTTACTCGA TTTGCCTCCTGTTGATATGGAAACGGGTGAAATTCTGACAGAGGAAGCTGTTCAAAATCTTCCACCTAT TCCAGAAGAAAGTGGGTGGAACCAGAAATCATCCTGCCTCAAGCTGAACTTAAATTCCCTGAACAGGA AGATGACTCAGATGACGAAGATGTTCAGGTCGATTTTTCAGCCAAAGAAGCCCTTGAATACAAACTTCC AAGCTTACAACTCTTTGCACCAGATAAACCAAAAGATCAGTCTAAAGAGAAGAAAATTGTCAGAGAAAA TATCAAAATCTTAGAAGCAACCTTTGCTAGCTTTGGTATTAAGGTAACAGTTGAACGGCCGAAATTGG ${\tt GCCATCAGTGACCAAGTATGAAGTCAAGCCGGCTGTTGGTGTAAGGGGTCAACCGCATTTCCAATCTATC}$ AGATGACCTCGCTCTAGCCTTGGCTGCCAAAGATGTCCGGATTGAAGCACCAATCCCTGGGAAATCCCT AATCGGAATTGAAGTGCCCAACTCCGATATTGCCACTGTATCTTTCCGAGAACTATGGGAACAATCGCA AACGAAAGCAGAAAATTTCTTGGAAATTCCTTTAGGGAAGGCTGTTAATGGAACCGCAAGAGCTTTTGA CCTTTCTAAAATGCCCCACTTGCTAGTTGCAGGTTCAACGGGTTCAGGGAAGTCAGTAGCAGTTAACGG CATTATTGCTAGCATTCTCATGAAGGCGAGACCAGATCAAGTTAAATTTATGATGGTCGATCCCAAGAT GGTTGAGTTATCTGTTTACAATGATATTCCCCACCTCTTGATTCCAGTCGTGACCAATCCACGCAAAGC CAGCAAGGCTCTGCAAAAGGTTGTGGATGAAATGGAAAACCGTTATGAACTCTTTGCCAAGGTGGGAGT TCGGAATATTGCAGGTTTTAATGCCAAGGTAGAAGAGTTCAATTCCCAGTCTGAGTACAAGCAAATTCC

GCTACCATTCATTGTCGTGATTGTGGATGAGTTGGCTGACCTCATGATGGTGGCCAGCAAGGAAGTGGAAGTGGAAGTTGTTGCATTGTTGGATTGTTGGCAGAAGGCGGTGCTGCAGGTATCCACATGATTCTTGCAACTCAGCGAGTGCTCTTGTTGATGTCATCTCTGGTTTGATTAAGGCCAATGTTCCATCTCGTGTAGCATTTTGCGGTTTCATCAGGAACAGACTCCCGTACGATTTTGGATGAAAATTGAGCAGAAAAAACTTCTTGGTCGAGGAGACATGTCTTTAAACCGATTGATGAAAATCATCCAGTTCGTCTCCAAGGCTCCTTTATCTCGGATGACGATGTTGAGCGCATTGTGAACTTCATCAAGACTCAGGCAGATGCAGACTACGATGAGAGTTTTGATCCAGGTGAGTTTCTGAAAAATGAAGGAAAATTCTCGGATGAGAGTGCTGGTGATCCGCTTTTTTGAAGAAGCTAAGTCTTTTGGTTATCAGAAACACAGAAAGCCAGTGCGTCTATGATTCAGCGTCGTTTATCAGTTGGATTTAACCCGTGCGACCCGTCTCATGGAAGAACCAGAAACCTGGAGATAGCAGGTGCTCATCGGTCCAGCTGAAGGTACCAAACCTCGAAAAGTGTTACAACAA

77

SP078 amino acid (SEQ ID NO:132)

RGFAKWWEGHERRKEERFVKQEEKARQKAEKEARLEQEETEKALLDLPPVDMETGEILTEEAVQNLPPI
PEEKWVEPEIILPQAELKFPEQEDDSDDEDVQVDFSAKEALEYKLPSLQLFAPDKPKDQSKEKKIVREN
IKILEATFASFGIKVTVERAEIGPSVTKYEVKPAVGVRVNRISNLSDDLALALAAKDVRIEAPIPGKSL
IGIEVPNSDIATVSFRELWEQSQTKAENFLEIPLGKAVNGTARAFDLSKMPHLLVAGSTGSGKSVAVNG
IIASILMKARPDQVKFMMVDPKMVELSVYNDIPHLLIPVVTNPRKASKALQKVVDEMENRYELFAKVGV
RNIAGFNAKVEEFNSQSEYKQIPLPFIVVIVDELADLMMVASKEVEDAIIRLGQKARAAGIHMILATQR
PSVDVISGLIKANVPSRVAFAVSSGTDSRTILDENGAEKLLGRGDMLFKPIDENHPVRLQGSFISDDDV
ERIVNFIKTQADADYDESFDPGEVSENEGEFSDGDAGGDPLFEEAKSLVIETQKASASMIQRRLSVGFN
RATRLMEELEIAGVIGPAEGTKPRKVLQQ

SP079 nucleotide (SEQ ID NO:133)

SP079 amino acid (SEQ ID NO:134)

QKEKENLVIAGKIGPEPEILANMYKLLIEENTSMTATVKPNFGKTSFLYEALKKGDIDIYPEFTGTVTE SLLQPSPKVSHEPEQVYQVARDGIAKQDHLAYLKPMSYQNTYAVAVPKKIAQEYGLKTISDLKKVEGQL KAGFTLEFNDREDGNKGLQSMYGLNLNVATIEPALRYQAIQSGDIQITDAYSTDAELERYDLQVLEDDK QLFPPYQGAPLMKEALLKKHPELERVLNTLAGKITESQMSQLNYQVGVEGKSAKQVAKEFLQEQGLLKK

SP080 nucleotide (SEQ ID NO:135)

SP080 amino acid (SEQ ID NO:136)

RSIEDHFDSNFELEYNLKEKGKTDLLKLVDKTTDMRLHFIRQTHPRGLGDAVLQAKAFVGNEPFVVMLG DDLMDITDEKAVPLTKQLMDDYERTHASTIAVMPVPHDEVSAYGVIAPQGEGKDGLYSVETFVEKPAPE DAPSDLAIIGRYLLTPEIFEILEKQAPGAGNEIQLTDAIDTLNKTQRVFAREFKGARYDVGDKFGFMKT SIDYALKHPQVKDDLKNYLIQLGKELTEKE

78

SP081 nucleotide (SEQ ID NO:137)

SP081 amino acid (SEQ ID NO:138)

AQNTRGVQLIEHVSPQMLKAQLESVFSDIPPQAVKTGMLATTEIMEIIQPYLKKLDCPYVLDPVMVATS GDALIDSNARDYLKTNLLPLATIITPNLPEAEEIVGFSIHDPEDMQRAGRLILKEFGPQSVVIKGGHLK GGAKDFLFTKNEQFVWESPRIQTCHTHGT

SP082 nucleotide (SEQ ID NO:139)

SP082 amino acid (SEQ ID NO:140)

 $IVQLEKDSKSDKEQVDKLFESFDASSDESISKLKELSETSLKTDAGKDYLNNKVKESSKAIVDFHLQKG\\ LAYDVKDSDDKFKDKATLETNVKEITKQIDFIKKVDETFKQENLEETLKSLNDLVDKYQKQIELLKKEE\\ EKAAEKAAEKAKESSSQSNSSGSASNESYNGSSNSNVDYSSSEQTNGYSNNYGGQDYSGSGDSSTNGGS\\ SEQYSSSNSNSGANNVYRYKGTGADGYQRYYYKDHNNGDVYDDDGNYLGNFGGGIAEPSQR$

SP083 nucleotide (SEQ ID NO:141)

TCTGACCAAGCAAAAGAAGCAGTCAATGACAAAGGAAAAGCAGCTGTTGTTAAGGTGGTGGAAAGCCA GGCAGAACTTTATAGCTTAGAAAAGAATGAAGATGCTAGCCTAAGAAAGTTACAAGCAGATGGACGCAT CACGGAAGAACAGGCTAAAGCTTATAAAGAATACAATGATAAAAAATGGAGGAGCAAATCGTAAAGTCAA TGAT

SP083 amino acid (SEQ ID NO:142)

LTKQKEAVNDKGKAAVVKVVESQAELYSLEKNEĎASLRKLQADGRITEEQAKAYKEYNDKNGGANRKVN D

SP084 nucleotide (SEQ ID NO:143)

GTCCGGCTCTGTCCAGTCCACTTTTTCAGCGGTAGAGGAACAGATTTTCTTTATGGAGTTTGAAGAACT
CTATCGGGAAACCCAAAAACGCAGTGTAGCCAGTCAGCAAAAGACTAGTCTGAACTTAGATGGGCAGAC
GCTTAGCAATGGCAGTCAAAAGTTGCCAGTCCCTAAAGGAATTCAGGCCCCATCAGGCCAAAGTATTAC
ATTTGACCGAGCTGGGGGCAATTCGTCCCTGGCTAAGGTTGAATTTCAGACCAGTAAAGGAGCGATTCG
CTATCAATTATATCTAGGAAATGGAAAAATTAAACGCATTAAGGAAACAAAAAAT

1

SP084 amino acid (SEQ ID NO:144)

 ${\tt SGSVQSTFSAVEEQIFFMEFEELYRETQKRSVASQQKTSLNLDGQTLSNGSQKLPVPKGIQAPSGQSITFDRAGGNSSLAKVEFQTSKGAIRYQLYLGNGKIKRIKETKN}$

79

SP085 nucleotide (SEQ ID NO:145)

 $\label{thm:constraint} GGGACAAATTCAAAAAATAGGCAAGAGGAAGCAAAAATCTTGCAAAAGGAAGAAGTCTTGAGGGTAGC\\ TAAGATGGCCCTGCAGACGGGGCAAAATCAGGTAAGCATCAACGGAGTTGAGATTCAGGTATTTTCTAG\\ TGAAAAAGGATTGGAGGTCTACCATGGTTCAGAACAGTTGTTGGCAATCAAAGAGCCA$

SP085 amino acid (SEQ ID NO:146)

GQIQKNRQEEAKILQKEEVLRVAKMALQTGQNQVSINGVEIQVFSSEKGLEVYHGSEQLLAIKEP

SP086 nucleotide (SEQ ID NO:147)

SP086 amino acid (SEQ ID NO:148)

 ${\tt RYQQQSEQKEWLLFVDQLEVELDRSQFEKVEGNRLYMKQDGKDIAIGKSKSDDFRKTNARGRGYQPMVY} \\ {\tt GLKSVRITEDNQLVRFHFQFQKGLEREFIYRVEKEKS}$

SP087 nucleotide (SEQ ID NO:149)

SP087 amino acid (SEQ ID NO:150)

NRQVAHYQDYALNKEKLVAFAMAKRTKDKVEQESGEQFFNLGQVSYQNKKTGLVTRVRTDKSQYEFLFP SVKIKEEKRDKKEEVATDSSEKVEKKKSEEKPEKKENS

SP088 nucleotide (SEQ ID NO:151)

SP088 amino acid (SEQ ID NO:152)

VVGWQYIPFPSKGSTIGPYPNGIRLEGFPKSEWYYFDKNGVLQEFVGWKTLEIKTKDSVGRKYGEKRED SEDKEEKRYYTNYYFNQNHSLETGWLYDQSNWYYLAKTEINGENYLGGERRAGWINDDSTWYYLDPTTG IMQTGWQYLGNKWYYLRSSGAMATGWYQEGTTWYYLDHPNGDMKTGWQNLGNKWYYLRSSGAMATGWYQ DGSTWYYLNAGNGDMKTGWFQVNGNWYYAYSSGALAVNTTVDGYSVNYNGEWVR

SP089 nucleotide (SEQ ID NO:153)

80

TAAAGGGAAGGACTATTATTTCAAATCCGGTGGTTATCTACTGACAAGTCAGTGGATTAATCAAGCTTA CATCAAAGAAAATGGAAACTATGCTGATAAAGAATGGATTTTCGAGAATGGTCACTATTATTATCTAAA ATCCGGTGGCTACATGGCAGCCAATGAATGGATTTGGGATAAGGAATCTTGGTTTTATCTCAAATTTGA TGGGAAAATGGCTGAAAAAGAATGGGTCTACGATTCTCATAGTCAAGCTTGGTACTACTTCAAATCCGG TGGTTACATGACAGCCAATGAATGGATTTGGGATAAGGAATCTTGGTTTTATCTCAAATCTGATGGGAA AATAGCTGAAAAAGAATGGGTCTACGATTCTCATAGTCAAGCTTGGTACTACTTCAAATCCGGTGGTTA CATGACAGCCAATGAATGGATTTGGGATAAGGAATCTTGGTTTTACCTCAAATCTGATGGGAAAATAGC TGAAAAAGAATGGGTCTACGATTCTCATAGTCAAGCTTGGTACTACTTCAAATCTGGTGGCTACATGGC GAAAAATGAGACAGTAGATGGTTATCAGCTTGGAAGCGATGGTAAATGGCTTGGAGGAAAAACTACAAA TGAAAATGCTGCTTACTATCAAGTAGTGCCTGTTACAGCCAATGTTTATGATTCAGATGGTGAAAAGCT TTCCTATATATCGCAAGGTAGTGTCGTATGGCTAGATAAGGATAGAAAAAGTGATGACAAGCGCTTGGC TATTACTATTTCTGGTTTGTCAGGCTATATGAAAACAGAAGATTTACAAGCGCTAGATGCTAGTAAGGA CTTTATCCCTTATTATGAGAGTGATGGCCACCGTTTTTATCACTATGTGGCTCAGAATGCTAGTATCCC AGTAGCTTCTCATCTTTCTGATATGGAAGTAGGCAAGAAATATTATTCGGCAGATGGCCTGCATTTTGA TGGTTTTAAGCTTGAGAATCCCTTCCTTTTCAAAGATTTAACAGAGGCTACAAACTACAGTGCTGAAGA ATTGGATAAGGTATTTAGTTTGCTAAACATTAACAATAGCCTTTTGGAGAACAAGGGCGCTACTTTTAA GGAAGCCGAAGAACATTACCATATCAATGCTCTTTATCTCCTTGCCCATAGTGCCCTAGAAAGTAACTG GGGAAGAAGTAAAATTGCCAAAGATAAGAATAATTTCTTTGGCATTACAGCCTATGATACGACCCCTTA CCTTTCTGCTAAGACATTTGATGATGTGGATAAGGGAATTTTAGGTGCAACCAAGTGGATTAAGGAAAA TTATATCGATAGGGGAAGAACTTTCCTTGGAAACAAGGCTTCTGGTATGAATGTGGAATATGCTTCAGA CCCTTATTGGGGCGAAAAATTGCTAGTGTGATGATGAAAATCAATGAGAAG

SP089 amino acid (SEQ ID NO:154)

AKSEWVEDKGAFYYLDQDGKMKRNAWVGTSYVGATGAKVIEDWVYDSQYDAWFYIKADGQHAEKEWLQI KGKDYYFKSGGYLLTSQWINQAYVNASGAKVQQGWLFDKQYQSWFYIKENGNYADKEWIFENGHYYYLK SGGYMAANEWIWDKESWFYLKFDGKMAEKEWVYDSHSQAWYYFKSGGYMTANEWIWDKESWFYLKSDGK IAEKEWVYDSHSQAWYYFKSGGYMTANEWIWDKESWFYLKSDGKIAEKEWVYDSHSQAWYYFKSGGYMA KNETVDGYQLGSDGKWLGGKTTNENAAYYQVVPVTANVYDSDGEKLSYISQGSVVWLDKDRKSDDKRLA ITISGLSGYMKTEDLQALDASKDFIPYYESDGHRFYHYVAQNASIPVASHLSDMEVGKKYYSADGLHFD GFKLENPFLFKDLTEATNYSAEELDKVFSLLNINNSLLENKGATFKEAEEHYHINALYLLAHSALESNW GRSKIAKDKNNFFGITAYDTTPYLSAKTFDDVDKGILGATKWIKENYIDRGRTFLGNKASGMNVEYASD PYWGEKIASVMMKINEK

SP090 nucleotide (SEQ ID NO:155)

SP090 amino acid (SEQ ID NO:156)

VFADDSEGWQFVQENGRTYYKKGDLKETYWRVIDGKYYYFDPLSGEMVVGWQYIPAPHKGVTIGPSPRI EIALRPDWFYFGQDGVLQEFVGKQVLEAKTATNTNKHHGEEYDSQAEKRVYYFEDQRSYHTLKTGWIYE EGHWYYLQKDGGFDSRINRLTVGELARGWVKDYPLTYDEEKLKAAPWYYLNPATGIMQTGWQYLGNRWY YLHSSGAMATGWYKEGSTWYYLDAENGDMRTGWQNLGNKWYYLRSSGAMATGWYQESSTWYYLNASNGD MKTGWFQVNGNWYYAYDSGALAVNTTVGGYYLNYNGEWVK

81

SP091 nucleotide (SEQ ID NO:157)

TGTCGCTGCAAATGAAACTGAAGTAGCAAAAACTTCGCAGGATACAACGACAGCTTCAAGTAGTTCAGA GCAAAATCAGTCTTCTAATAAAACGCAAACGAGCGCAGAAGTACAGACTAATGCTGCTGCCCACTGGGA TGGGGATTATTATGTAAAGGATGATGGTTCTAAAGCTCAAAGTGAATGGATTTTTGACAACTACTATAA ATCAGGTGGATATATGGCCCAAAACGAGTGGATCTATGACAGTAATTACAAGAGTTGGTTTTATCTCAA GGGTTACATGGCTAAAAGCCAATGGCAAGGAAGTTATTTCTTGAATGGTCAAGGAGCTATGATGCAAAA TGAATGGCTSCTATGATCCAGCCTATTCTGCTTATTTTTATCTAAAATCCGATGGAACTTATGCTAACC AAGAGTGGCAAAAAGTGGGCGCAAATGGTACTATTTCAAGAAGTGGGGCTATATGGCTCGGAATGAGT ATGGTAAGCGCTATTTCTTTAATAATAGAGAAGAACAAGTGGGAACCGAACATGCTAAGAAAGTCATTG ATATTAGTGAGCACAATGGTCGTATCAATGATTGGAAAAAGGTTATTGATGAGAACGAAGTGGATGGTG TCATTGTTCGTCTAGGTTATAGCGGTAAAGAAGACAAGGAATTGGCGCATAACATTAAGGAGTTAAACC GTCTGGGAATTCCTTATGGTGTCTATCTCTATACCTATGCTGAAAATGAGACCGATGCTGAGAGTGACG AGAATTGGGAATATGTAAATAAGAGCAAGAGAGCTCCAAGTGATACAGGCACTTGGGTTAAAATCATCA ACAAGTĀCATGGACACGĀTGAAGCAGGCGGGTTATCAAAATGTGTATGTCTATAGCTATCGTAGTTTAT TACAGACGCGTTTAAAACACCCAGATATTTTAAAACATGTAAACTGGGTAGCGGCCTATACGAATGCTT TAGAATGGGAAAACCCTCATTATTCAGGAAAAAAAGGTTGGCAATATACCTCTTCTGAATACATGAAAG GAATCCAAGGGCGCGTAGATGTCAGCGTTTGGTAT

SP091 amino acid (SEQ ID NO:158)

VAANETEVAKTSQDTTTASSSSEQNQSSNKTQTSAEVQTNAAAHWDGDYYVKDDGSKAQSEWIFDNYYK
AWFYINSDGRYSQNEWHGNYYLKSGGYMAQNEWIYDSNYKSWFYLKSDGAYAHQEWQLIGNKWYYFKKW
GYMAKSQWQGSYFLNGQGAMMQNEWLYDPAYSAYFYLKSDGTYANQEWQKVGGKWYYFKKWGYMARNEW
QGNYYLTGSGAMATDEVIMDGTRYIFAASGELKEKKDLNVGWVHRDGKRYFFNNREEQVGTEHAKKVID
ISEHNGRINDWKKVIDENEVDGVIVRLGYSGKEDKELAHNIKELNRLGIPYGVYLYTYAENETDAESDA
KQTIELIKKYNMNLSYPIYYDVENWEYVNKSKRAPSDTGTWVKIINKYMDTMKQAGYQNVYVYSYRSLL
QTRLKHPDILKHVNWVAAYTNALEWENPHYSGKKGWQYTSSEYMKGIQGRVDVSVWY

SP092 nucleotide (SEQ ID NO:159)

TACGTCTCAGCCTACTTTTGTAAGAGCAGAAGAATCTCCACAAGTTGTCGAAAAATCTTCATTAGAGAA AGAAGACGCTCAGAAAAAGTATGAAGATGATCAGAAGAGAACTGAGGAGAAAGCTCGAAAAAGAAGCAGA AGCATCTCAAAAATTGAATGATGTGGCGCTTGTTGTTCAAAATGCATATAAAGAGTACCGAGAAGTTCA AAATCAACGTAGTAAATATAAATCTGACGCTGAATATCAGAAAAAATTAACAGAGGTCGACTCTAAAAT TGAACCAAATGCGTTGGCTGAGACTAAGAAAAAAGCAGAAGAAGCTAAAGCAGAAGAAAAAGTAGCTAA GAGAAAATATGATTATGCAACTCTAAAGGTAGCACTAGCGAAGAAGAAGTAGAGGCTAAGGAACTTGA AATTGAAAAACTTCAATATGAAATTTCTACTTTGGAACAAGAAGTTGCTACTGCTCAACATCAAGTAGA TAATTTGAAAAACTTCTTGCTGGTGCGGATCCTGATGATGGCACAGAAGTTATAGAAGCTAAATTAAA TCTTGACAGCCTTGATCCTGAAGGTAAGACTCAGGATGAATTAGATAAAGAAGCAGAAGAAGCTGAGTT GGATAAAAAAGCTGATGAACTTCAAAATAAAGTTGCTGATTTAGAAAAAGAAATTAGTAACCTTGAAAT ATTACTTGGAGGGGCTGATNCTGAAGATGATACTGCTGCTCTTCAAAATAAATTAGCTACTAAAAAAAGC TGAATTGGAAAAACTCAAAAAGAATTAGATGCAGCTCTTAATGAGTTAGGCCCTGATGGAGATGAAGA AGAAACTCCAGCGCCGGCTCCTCAACCAGAGCAACCAGCTCCTGCACCAAAACCAGAGCAACCAGCTCC AGCTCCAAAACCAGAGCAACCAGCTCCTGCACCAAAACCAGAGCAACCAGCTCCAGCTCCAAAACCAGA GCAACCAGCTCCAGCTCCAAAACCAGAGCAACCAGCTAAGCCGGAGAAACCAGCTGAAGAGCCTACTCA ACCAGAAAAACCAGCCACTCCAAAAACAGGCTGGAAACAAGAAAACGGTATGTGGTATTTCTACAATAC TGATGGTTCAATGGCAATAGGTTGGCTCCAAAACAACGGTTCATGGTACTACCTAAACGCTAACGGCGC TATGGCAACAGGTTGGGTGAAAGATGGAGATACCTGGTACTATCTTGAAGCATCAGGTGCTATGAAAGC AAGCCAATGGTTCAAAGTATCAGATAAATGGTACTATGTCAACAGCAATGGCGCTATGGCGACAGGCTG GCTCCAATACAATGGCTCATGGTACTACCTCAACGCTAATGGTGATATGGCGACAGGATGGCTCCAATA CAACGGTTCATGGTATTACCTCAACGCTAATGGTGATATGGCGACAGGATGGGCTAAAGTCAACGGTTC ATGGTACTACCTAAACGCTAACGGTGCTATGGCTACAGGTTGGGCTAAAGTCAACGGTTCATGGTACTA

CCTAAACGCTAACGGTTCAATGGCAACAGGTTGGGTGAAAGATGGAGATACCTGGTACTATCTTGAAGC

 ${\tt ATCAGGTGCTATGAAAGCAAGCCAATGGTTCAAAGTATCAGATAAATGGTACTATGTCAATGGCTTAGGTGCCTTGCAGTCAACACAACTGTAGATGGCTATAAAGTCAATGCCAATGGTGAATGGGTT$

SP092 amino acid (SEQ ID NO:160)

TSQPTFVRAEESPQVVEKSSLEKKYEEAKAKADTAKKDYETAKKKAEDAQKKYEDDQKRTEEKARKEAE
ASQKLNDVALVVQNAYKEYREVQNQRSKYKSDAEYQKKLTEVDSKIEKARKEQQDLQNKFNEVRAVVVP
EPNALAETKKKAEEAKAEEKVAKRKYDYATLKVALAKKEVEAKELEIEKLQYEISTLEQEVATAQHQVD
NLKKLLAGADPDDGTEVIEAKLKKGEAELNAKQAELAKKQTELEKLLDSLDPEGKTQDELDKEAEEAEL
DKKADELQNKVADLEKEISNLEILLGGADXEDDTAALQNKLATKKAELEKTQKELDAALNELGPDGDEE
ETPAPAPQPEQPAPAPKPEQPAPAPKPEQPAPAPKPEQPAPAPKPEQPAPAPKPEQPAKPEKPAEEPTQ
PEKPATPKTGWKQENGMWYFYNTDGSMAIGWLQNNGSWYYLNANGAMATGWVKDGDTWYYLEASGAMKA
SQWFKVSDKWYYVNSNGAMATGWLQYNGSWYYLNANGDMATGWLQYNGSWYYLNANGDMATGWAKVNGS
WYYLNANGAMATGWAKVNGSWYYLNANGSMATGWVKDGDTWYYLEASGAMKASQWFKVSDKWYYVNGLG
ALAVNTTVDGYKVNANGEWV

P093 nucleotide (SEQ ID NO:161)

TGGACAGGTGAAAGGTCATGCTACATTTGTGAAATCCATGACAACTGAAATGTACCAAGAACAACAGAACCATTGTCTCTCGCCTACAATCAACGCTTGGNTTCGCAAAATCGCATTGTAGATCCTTTTTTTGGCGGAGGGATTGTAGGTCAATTACCAAGTGTTGTCTACCAAGTTTTTTGGCGGAGGGATTGTAGGTCAATTACCAAGTTTTTTGGAGCCGGTTTATTTGGGAGCCAGATTATCATCATTTAGGGATGGGCTTGGCTCATGTGATGGAAATCATGGAGCCGGTTTATTTGGGAGCAGGATTCCTCAGTGATTGCTGGGCACCGTGCAGAGCCAAGCCAAGCCAAGCCTTTTTTTCCGCCATTTGGATCAGCTAAAAAGTTGGAGATGCTCTTTATTATGATAATGGCCAGGAAATTGTAGAATATCAGATGAACACAGGATTATTTTACCGTCGGAATGGGAAAAATTAGAATCGGTTAGCTCTAAAAAAATTAGATAACCTGCGATCCGATTCCTACCTTTAATAAAACGCTTATTAGTGAATTTTTGAACGAGGTCGCTGTTTATCAAAAAATCAGATCCACAAACAGCTGCAGTTGCGAGGGTTGCTTTTACCAAAAAATCAGATCCACAAACAGCTGCAGTTGCGAGGGTTGCTTTTACCAAAAAATCAGATCCACAAACAGCTGCAGTTGCGAGGGTTGCTTTTACCAAAAAATCAGATCCACAAACAGCTGCAGTTGCGAGGGTTGCTTTTACCGAAAGAAGGACAATCTGTATCGCGTGTTGCAACCTCTCAATGGTTG

SPO93 amino acid (SEQ ID NO:162)

GQVKGHATFVKSMTTEMYQEQQNHSLAYNQRLXSQNRIVDPFLAEGYEVNYQVSDDPDAVYGYLSIPSL EIMEPVYLGADYHHLGMGLAHVDGTPLPLDGTGIRSVIAGHRAEPSHVFFRHLDQLKVGDALYYDNGQE IVEYQMMDTEIILPSEWEKLESVSSKNIMTLITCDPIPTFNKRLLVNFERVAVYQKSDPQTAAVARVAF TKEGQSVSRVATSQWL

SP094 nucleotide (SEQ ID NO:163)

SP094 amino acid (SEQ ID NO:164)

IAPLKDLRETMLEIASGAQNLRAKEVGAYELREVTRQFNAMLDQIDQLMVAIRSQEETTRQYQLQALSS QINPHFLYNTLDTIIWMAEFHDSQRVVQVTKSLATYFRLALNQGKDLICLSDEINHVRQYLFIQKQRYG DKLEYEINENVAFDNLVLPKLVLQPLVENALYHGIKEKEGQGHIKLSVQKQDSGLVIRIEDDGVGFQDA GDSSQSQLKRGGVGLQNVDQRLKLHFGANYHMKIDSRPQKGTKVEIYINRIETS

SP095 nucleotide (SEQ ID NO:165)

GACAGAATCTAAAGAATCTGGAATTAAACAAATGGACAATGTCATAAAATATTTTGAGTTTATTGAATC TAAAAGTATTGCTTTATATTTTCAAAAACGATTAAATGAGCTGATAGAT

SP095 amino acid (SEQ ID NO:166)

RSYGTFFLOONRLHNIYKGFTHYKYYRAENSHLIYADYFEMKLKKLLKDDTKVFEKSTFKFVEGYKIYL TESKESGIKOMDNVIKYFEFIESKSIALYFQKRLNELID

SP096 nucleotide (SEQ ID NO:167)

CAACGTTGAGAATTATTTGCGAATGTGTTTGGATAGCATTCAGAATCAGACGTATCAAAATTTTGAGTG TTTATTAATCAATGATGGCTCTCCAGATCATTCATCCAAAATATGTGAAGAATTTGTAGAGAAAGATTC TCGTTTCAAATATTTTGAGAAAGCAAACGGCGGTCTTTCATCAGCTCGTAACCTAGGTATTGAATGTTC GGGGGGGGCGTACATTACTTTTGTAGACTC

SP096 amino acid (SEQ ID NO:168)

NVENYLRMCLDSIQNQTYQNFECLLINDGSPDHSSKICEEFVEKDSRFKYFEKANGGLSSARNLGIECS GGGVHYFCRL

SP097 nucleotide (SEQ ID NO:169)

CTACTATCAATCAAGTTCTTCAGCCATTGAGGCCACCATTGAGGGCAACAGCCAAACGACCATCAGCCA GACTAGCCACTTTATTCAGTCTTATATCAAAAAACTAGAAACCACCTCGACTGGTTTGACCCAGCAGAC GGATGTTCTGGCCTATGCTGAGAATCCCAGTCAAGACAAGGTCGAGGGAATCCGAGATTTGTTTTTGAC ${\tt CATCTTGAAGTCAGATAAGGACTTGAAAACTGTTGTGCTGGTGACCAAATCTGGTCAGGTCATTTCTAC}$ $A {\tt GATGACAGTGTGCAGATGAAAACTTCCTCTGATATGATGGCTGAGGATTGGTACCAAAAGGCCATTCA}$ ${\tt TCAGGGAGCTATGCCTGTTTTGACTCCAGCTCGTAAATCAGATAGTCAGTGGGTCATTTCTGTCACTCA}$ ${\tt AGCCTATCTCAATCAACTCCAGTTGGGGCAGCAGGGCTTTGCCTTCATTATCAATGAAAACCATGAATT}$ TGTCTACCATCCTCAACACACACTTTATAGTTCGTCTAGCAAAATGGAGGCTATGAAACCCTACATCGA GACGGTGCTTGGCGTGTCATCATTGGAAAAGTTAGACCAGGTTCGGAGTCAG

SP097 amino acid (SEQ ID NO:170)

 ${\tt YYQSSSSAIEATIEGNSQTTISQTSHFIQSYIKKLETTSTGLTQQTDVLAYAENPSQDKVEGIRDLFLT}$ $\verb|ILKSDKDLKTVVLVTKSGQVISTDDSVQMKTSSDMMAEDWYQKAIHQGAMPVLTPARKSDSQWVISVTQ|$ ELVDAKGANLGVLRLDISYETLEAYLNQLQLGQQGFAFIINENHEFVYHPQHTVYSSSSKMEAMKPYID TGQGYTPGHKSYVSQEKIAGTDWTVLGVSSLEKLDQVRSQ

SP098 nucleotide (SEQ ID NO:171)

GACAAAAACATTAAAACGTCCTGAGGTTTTATCACCTGCAGGGACTTTAGAGAAGCTAAAGGTAGCTGT TCAGTATGGAGCAGATGCTGTCTTTATCGGTGGTCAGGCCTATGGTCTTCGTAGCCGTGCGGGAAACTT TACTTTCGAACAGATGGAAGAAGGCGTGCAGTTTGCGGCCAAGTATGGTGCCAAGGTCTATGTAGCGGC TAATATGGTTATGCACGAAGGAAATGAAGCTGGTGCTGGTGAGTGGTTCCGTAAACTGCGTGATATCGG GATTGCAGCAGTTATCGTATCTGACCCAGCCTTGATTATGATTGCAGTGACTGAAGCACCAGGCCTTGA AATCCACCTTTCTACCCAAGCCAGTGCCACTAACTATGAAACCCTTGAGTTCTGGAAAGAGCTAGGCTT GACTCGTGTCGTTTTAGCGCGTGAGGTTTCAATGGAAGAATTAGCTGAGATCCGCAAACGTACAGATGT TGAAATTGAAGCCTTTGTCCATGGAGCTATGTGTATTTCATACTCTGGACGTTGTACTCTTTCAAACCA CATGAGTATGCGTGATGCCAACCGTGGTGGATGTTCTCAGTCATGCCGTTGGAAATACGACCTTTACGA TATGCCATTTGGGAAAGAACGTAAGAGTTTGCAGGGTGAGATTCCAGAAGAATTTTCAATGTCAGCCGT TGACATGTCTATGATTGACCANATTCCAGATATGATTGAAAATGGTGTGGACAGTCTAAAAATCGAAGG ACGTATGNAGTCTATTCACTANGTATCAACAGTAACCAACTGCTACAAGGCGGCTGTGGATGCCTATCT TGAAAGTCCTGAAAAGTTTGAAGCTATCAAACAAGACTTGGTGGACGAGGTTGCCCAACG TGAACTGGCTACAGGATTTTACTATGGTACACCATCTGAAAATGAGCAGTTGTTTTGGTGCTCGTAA AATCCCTGAGTACAAGTTTGTCGCTGAAGTGGTTTCTTATGATGATGCGGCACAAACAGCAACTATTCG ${\tt TCAACGAAACGTCATTAACGAAGGGGACCAAGTTGAGTTTATGGTCCAGGTTTCCGTCATTTTGAAAC}$ $\verb|CTATATTGAAGATTTGCATGATGCTAAAGGCAATAAAATCGACCGCGCTCCAAATCCAATGGAACTATT| \\$ ${\tt GACTATTAAAGTCCCACAACCTGTTCAATCAGGAGACATGGTTCGAGCTCTTAAAGAGGGGCTTATCAA}$ TCTTTATAAGGAAGATGGAACCAGCGTCACAGTTCGTGCT

SP098 amino acid (SEQ ID NO:172)

TKTLKRPEVLSPAGTLEKLKVAVQYGADAVFIGGQAYGLRSRAGNFTFEQMEEGVQFAAKYGAKVYVAA NMVMHEGNEAGAGEWFRKLRDIGIAAVIVSDPALIMIAVTEAPGLEIHLSTQASATNYETLEFWKELGL TRVVLAREVSMEELAEIRKRTDVEIEAFVHGAMCISYSGRCTLSNHMSMRDANRGGCSQSCRWKYDLYD MPFGKERKSLQGEIPEEFSMSAVDMSMIDXIPDMIENGVDSLKIEGRMXSIHXVSTVTNCYKAAVDAYL ESPEKFEAIKQDLVDEMWKVAQRELATGFYYGTPSENEQLFGARRKIPEYKFVAEVVSYDDAAQTATIR QRNVINEGDQVEFYGPGFRHFETYIEDLHDAKGNKIDRAPNPMELLTIKVPQPVQSGDMVRALKEGLIN LYKEDGTSVTVRA

84

SP099 nucleotide (SEQ ID NO:173)

SP099 amino acid (SEQ ID NO:174)

SQETFKNITNSFSMQINRRVNQGTPRGAGNIKGEDIKKITENKAIESYVKRINAIGDLTGYDLIETPET KKNLTADRAKRFGSSLMITGVNDSSKEDKFVSGSYKLVEGEHLTNDDKDKILLHKDLAAKHGWKVGDKV KLDSNIYDADNEKGAKETVEVTIKGLFDGHNKSAVTYSQELYENTAITDIHTAAKLYGYTEDTAIYGDA TFFVTADKNLDDVMKELNGISGINWKSYTLVKSSSNYPALEQSISGMYKMAN

SP100 nucleotide (SEQ ID NO:175)

SP100 amino acid (SEQ ID NO:176)

VNAQSNSLILIDEPEISLHPSAIYKFKEFLLQECLNKKHQIIITTHSTQLIKDFPREAVKLLVKNGEKV DVIENIDYQDAFFELGDVYHSRKMIYVEDRLAKYILEFVITHSGSENLKQNLVVRYIPGGANQIICNNI LNSSYLDSDNHYFWLDGDQNTNVSESNNLMNYLENGVVISDKIPESDNKNLDDIIKLIXGCPIKFNVSG NKGQKNNIELIAKQRSFIDYWAKY

SP101 nucleotide (SEQ ID NO:177)

TTACCGCGTTCATCAAGATGTCAAACAAGTCATGACCTATCAACCCATGGTGCGAGAAATATTGAGTGA ACAAGACACCCCAGCAAACGAAGCACTTGTGCTTGCTATGATTTATACTGAAACAAAAGGAAAAGAAGG ACAAGACACCCCAGCAACACGAAGACTTGTGCTTGCTATGATTATACTGAAACAAAAGGAAAAGAAGG CGATGTTATGCAGTCTAGCATGTTATCCACCAACACCATCAATGATAATGCCTCTAGCAT TCGGCAAGGCATTCAAACTCTGACAGCCAATCTCTATCTGGCGCAGAAGAAGAGGGGTAGATATCTGGAC AGCTGTTCAAGCCTATAATTTTGGACCTGCCTATATCGATTTTATCGCCCAAAATGGCAAGGAAAATAC CCTGGCTCTAGCCAAACAGTACTCTCGTGAGACTGTTGCCCCCTTTGCTTAGTAAATAGGACTGGAAAGAC TTATAGTTATATTCACCCCATTTCCATTTTTCACGGTGCTGAACTCTATGTAAATGGAGGAAACTATTA TTATTCTAGACAGGTACGACTTTACATCATCATCAAATGTTTCACTCTCTTTTCAACATCTGGC

WO 98/18930 PCT/US97/19422

Table 1 85

SP101 amino acid (SEQ ID NO:178)

YRVHQDVKQVMTYQPMVREILSEQDTPANEELVLAMIYTETKGKEGDVMQSSESASGSTNTINDNASSI RQGIQTLTGNLYLAQKKGVDIWTAVQAYNFGPAYIDFIAQNGKENTLALAKQYSRETVAPLLGNRTGKT YSYIHPISIFHGAELYVNGGNYYYSRQVRLNLYIIKCFTLFSTSG

SP102 nucleotide (SEQ ID NO:179)

SP102 amino acid (SEQ ID NO:180)

WMGFNYLRIRRAAKIVDNEEFEALIRTGQLIDLRDPAEFHRKHILGARNIPSSQLKTSLAALRKDKPVL LYENQRAQRVTNAALYLKKQGFSEIYILSYGLDSWKGKVKTS

SP103 nucleotide (SEQ ID NO:181)

ACTAAACCAGCATCGTTCGCAGGAAAATAAGGACAATAATCGTGTCTCTTATGTGGATGGCAGCCAGTC TGTAATCAAAATTACAGATCAGGGCTATGTAACGTCACACGGTGACCACTATCATTACTATAATGGGAA AGTTCCTTATGATGCCCTCTTTAGTGAAGAACTCTTGATGAAGGATCCAAACTATCAACTTAAAGACGC TGATATTGTCAATGAAGTCAAGGGTGGTTATATCATCAAGGTCGATGGAAAATATTATGTCTACCTGAA AGATAATGAGAAGGTTAACTCTAATGTTGCTGTAGCAAGGTCTCAGGGACGATATACGACAAATGATGG TTATGTCTTTAATCCAGCTGATATTATCGAAGATACGGGTAATGCTTATATCGTTCCTCATGGAGGTCA AAAAAATATGCAACCGAGTCAGTTAAGCTATTCTTCAACAGCTAGTGACAATAACACGCAATCTGTAGC AAAAGGATCAACTAGCAAGCCAGCAAATAAATCTGAAAATCTCCAGAGTCTTTTGAAGGAACTCTATGA TTCACCTAGCGCCCAACGTTACAGTGAATCAGATGGCCTGGTCTTTGACCCTGCTAAGATTATCAGTCG TACACCAAATGGAGTTGCGATTCCGCATGGCGACCATTACCACTTTATTCCTTACAGCAAGCTTTCTGC CTTAGAAGAAAGATTGCCAGAATGGTGCCTATCAGTGGAACTGGTTCTACAGTTTCTACAAATGCAAA ACCTAATGAAGTAGTGTCTAGTCTAGGCAGTCTTTCAAGCAATCCTTCTTCTTTAACGACAAGTAAGGA GCTCTCTTCAGCATCTGATGGTTATATTTTTAATCCAAAAGATATCGTTGAAGAAACGGCTACAGCTTA TATTGTAAGACATGGTGATCATTTCCATTACATTCCAAAATCAAATCAAATTGGGCAACCGACTCTTCC AGAAGATGGATACGGATTTGATGCTAATCGTATTATCGCTGAAGATGAATCAGGTTTTGTCATGAGTCA CGGAGACCACAATCATTATTTCTTCAAGAAG

SP103 amino acid (SEQ ID NO:182)

LNQHRSQENKDNNRVSYVDGSQSSQKSENLTPDQVSQKEGIQAEQIVIKITDQGYVTSHGDHYHYYNGK VPYDALFSEELLMKDPNYQLKDADIVNEVKGGYIIKVDGKYYVYLKDAAHADNVRTKDEINRQKQEHVK DNEKVNSNVAVARSQGRYTTNDGYVFNPADIIEDTGNAYIVPHGGHYHYIPKSDLSASELAAAKAHLAG KNMQPSQLSYSSTASDNNTQSVAKGSTSKPANKSENLQSLLKELYDSPSAQRYSESDGLVFDPAKIISR TPNGVAIPHGDHYHFIPYSKLSALEEKIARMVPISGTGSTVSTNAKPNEVVSSLGSLSSNPSSLTTSKE LSSASDGYIFNPKDIVEETATAYIVRHGDHFHYIPKSNQIGQPTLPNNSLATPSPSLPINPGTSHEKHE EDGYGFDANRIIAEDESGFVMSHGDHNHYFFKK

SP105 nucleotide (SEQ ID NO:183)

TGACTACCTTGAAATCCCACTTTACAGCTATCTTGGTGGATTCAACACTAAAGTTCTTCCAACTCCAAT GATGAACATCATCAACGGTGGTTCTCACTCTTGACGCTCCAATCGCTTTCCAAGAGTTCATGATCTTGCC AGTTGATCATCAACACACTTTAAAGAAGCCCTTCGTTACGGTGCTGAAATCTTCCACGCTCTTAAGAAAAAT CCTTAAATCACGTGGTTTTGGAAACTGCCGTAGGTGACGAAGGTGGATTCGCTCCTCGTTTCGAAGGAAC TGAAGATGGTGTTGAAACTATCCTTGCTGCAATTTGAAGCTGCTGGATATGTACCAGGTAAAGACGTATT TATCGGATTTGACTTCATCAGAATTCTACGATAAAGACGTAAAGTTTACGACTACACTAAATT TGAAGGTGAAGGTGCTGCTGCTACATCTGCAGAACAAATCGACTACCTTGAAGAATTGGTTAACAA ATACCCAATCATCACTATTGAAGATGGTTATGGATGAAAACGACTGGGATGGTTGGAAAGCTCTTACTGA ACGTCTTGGTAAGAAACTACCTTGCACACCTTGCACGC

TGGTATCCAAGAAGGTGCTGCTAACTCAATCCTTATCAAAGTTAACCAAATCGGTACTCTTACTGAAAC TTTTGAAGCTATCGAAATGGCTAAAGAAGCTGGTTACACTGCTGTTGTATCACACCGTTCAGGTGAAAC TGAAGATTCAACAATCGCTGATATTGCAGTTGCAACTAACGCAGGACAAATCAAGACTGGTTCACTTTC ACGTACAGACCGCATCGCTAAATACAACCAATTGCTTCGTATCGAAGACCAACTTGGTGAAGTAGCTGA ATATCGTGGATTGAAATCAACCTTAAAAAAA

86

SP105 amino acid (SEQ ID NO:184)

DYLEIPLYSYLGGFNTKVLPTPMMNIINGGSHSDAPIAFQEFMILPVGAPTFKEALRYGAEIFHALKKI LKSRGLETAVGDEGGFAPRFEGTEDGVETILAAIEAAGYVPGKDVFIGFDCASSEFYDKERKVYDYTKF EGEGAAVRTSAEQIDYLEELVNKYPIITIEDGMDENDWDGWKALTERLGKKVQLVGDDFFVTNTDYLAR GIQEGAANSILIKVNQIGTLTETFEAIEMAKEAGYTAVVSHRSGETEDSTIADIAVATNAGQIKTGSLS RTDRIAKYNQLLRIEDQLGEVAEYRGLKSFYNLKK

SP106 nucleotide (SEQ ID NO:185)

SP106 amino acid (SEQ ID NO:186)

RIFFWSNVRVEGHSMDPTLADGEILFVVKHLPIDRFDIVVAHEEDGNKDIVKRVIGMPGDTIRYENDKL YINDKETDEPYLADYIKRFKDDKLQSTYSGKGFEGNKGTFFRSIAQKAQAFTVDVNYNTNFSFTVPEGE YLLLGDDRLVSSDSRHVGTFKAKDITGEAKFRLWPITRIGTF

SP107 nucleotide (SEQ ID NO:187)

SP107 amino acid (SEQ ID NO:188)

DSLKDVKANASDSKPAQDKKDAKQGTEDSKDSDKMTETNSVPAGVIVVSLLALLGVIAFWLIRRKKESE IQQLSTELIKVLGQLDAEKADKKVLAKAQNLLQETLDFVKEENGSAETETKLVEELKAILDKLK

SP108 nucleotide (SEQ ID NO:189)

ATCGCTTAGTCAGCAGACTATAATCCAGTCCTTCAATGCTCAAACAGAATTTATCCAAAGATTGCGTGA GGCTCATGACAACTACTCAGGCTATTCTCAGTCAGCCATCTTTTATTCTTCAACGGTCAATCCTTCGAC TCGCTTTGTAAATGCACTCATTTATGCCCTTTTAGCTGGAGTAGGAGCTTATCGTATCATGATGGGTTC ${\tt AGCCTTGACCGTCGGTCGTTTAGTGACTTTTTTGAACTATGTTCAGCAATACACCAAGCCCTTTAACGA}$ TATTTCTTCAGTGCTAGCTGAGTTGCAAAGTGCTCTGGCTTGCGTAGAGCGTATCTATGGAGTCTTAGA TAGCCCTGAAGTGGCTGAAACAGGTAAGGAAGTCTTGACGACCAGTGACCAAGTTAAGGGAGCTATTTC CTTTAAACATGTCTCTTTTGGCTACCATCCTGAAAAATTTTGATTAAGGACTTGTCTATCGATATTCC AGCTGGTAGTAAGGTAGCCATCGTTGGTCCGACAGGTGCTGGAAAATCAACTCTTATCAATCTCCTTAT GCGTTTTTATCCCATTAGCTCGGGAGATATCTTGCTGGATGGGCAATCCATTTATGATTATACACGAGT $\tt ATCATTGAGACAGCAGTTTGGTATGGTGCTTCAAGAAACCTGGCTCACACAAGGGACCATTCATGATAA.$ TATTGCCTTTGGCAATCCTGAAGCCAGTCGAGAGCAAGTAATTGCTGCCGAAAGCAGCTAATGCAGA $\verb|CTTTTCATCCAACAGTTGCCACAGGGATACGATACCAAGTTGGAAAATGCTGGAGAATCTCTCTGT| \\$ $\tt CGGCCAAGCTCAGCTCTTGACCATAGCCCGAGTCTTTCTGGCTATTCCAAAGATTCTTATCTTAGACGA$ ${\tt GGCAACTTCTTCCATTGATACACGGACAGAAGTGCTGGTACAGGATGCCTTTGCAAAACTCATGAAGGG}$ CCGCACAAGTTTCATCATTGCTCACCGTTTGTCAACCATTCAGGATGCGGATTTAATTCTTGTCTTAGT

AGATGGTGATATTGTTGAATATGGTAACCATCAAGAACTCATGGATAGAAAGGGTAAGTATTACCAAAT GCAAAAGCTGCGGCTTTTAGTTCTGA

87

SP108 amino acid (SEQ ID NO:190)

KKSYHLFQKQTETRGIQTQLIEESLSQQTIIQSFNAQTEFIQRLREAHDNYSGYSQSAIFYSSTVNPST ${\tt RFVNALIYALLAGVGAYRIMMGSALTVGRLVTFLNYVQQYTKPFNDISSVLAELQSALACVERIYGVLD}$ SPEVAETGKEVLTTSDQVKGAISFKHVSFGYHPEKILIKDLSIDIPAGSKVAIVGPTGAGKSTLINLLM RFYPISSGDILLDGQSIYDYTRVSLRQQFGMVLQETWLTQGTIHDNIAFGNPEASREQVIAAAKAANAD FFIQQLPQGYDTKLENAGESLSVGQAQLLTIARVFLAIPKILILDEATSSIDTRTEVLVQDAFAKLMKG RTSFIIAHRLSTIQDADLILVLVDGDIVEYGNHQELMDRKGKYYQMQKAAAFSSE

SP109 nucleotide (SEQ ID NO:191)

ACGAAATGCAGGGCAGACAGATGCCTCGCAAATTGAAAAGGCGGCAGTTAGCCAAGGAGGAAAAGCAGT GAAAAAAACAGAAATTAGTAAAGACGCAGACTTGCACGAAATTTATCTAGCTGGAGGTTGTTTCTGGGG AGTGGAGGAATATTTCTCACGTGTTCCCGGGGTGACGGATGCCGTTTCAGGCTATGCAAATGGTAGAGG AGAAACAACCAAGTACGAATTGATTAACCAAACAGGTCATGCAGAAACCGTCCATGTCACCTATGATGC CAAGCAAATTTCTCTCAAGGAAATCCTGCTTCACTATTTCCGCATTATCAATCCAACCAGCAAAAAATAA ${\tt ACAAGGAAATGATGTGGGGACCCAGTACCGTACTGGTGTTTATTACACAGATGACAAGGATTTGGAAGT}$ GATTAACCAAGTCTTTGATGAGGTGGCTAAGAAATACGATCAACCTCTAGCAGTTGAAAAAGGAAAACTT GAAGAATTTTGTGGTGGCTGAGGATTACCATCAAGACTATCTCAAGAAAAATCCAAAATGGCTACTGCCA TATCAATGTTAATCAGGCGGCCTATCCTGTCATTGATGCCAGCAAATATCCAAAACCAAGTGATGAGGA ATTGAAAAAGACCCTGTCACCTGAGGAGTATGCAGTTACCCAGGAAAATCAAACAGAACGAGCTTTCTC AAACCGTTACTGGGATAAATTTGAATCCGGTATCTATGTGGATATAGCAACTGGGGAACCTCTCTTTTC ATCAAAAGACAAATTTGAGTCTGGTTGTGGCCTGGCCTAGTTTTACCCAACCCATCAGTCCAGATGTTGT CACCTACAAGGAAGATAAGTCCTACAATATGACGCGTATGGAAGTGCGGAGCCGAGTAGGAGATTCTCA CCTTGGGCATGTCTTACGGATGGTCCACAGGACAAGGGCGGCTTACGTTACTGTATCAATAGCCTCTC TATCCGCTTTATTCCCAAAGACCAAATGGAAGAAAAAGGCTACGCTTATTTACTAGATTATGTTGAT

SP109 amino acid (SEQ ID NO:192)

RNAGQTDASQIEKAAVSQGGKAVKKTEISKDADLHEIYLAGGCFWGVEEYFSRVPGVTDAVSGYANGRG ETTKYELINQTGHAETVHVTYDAKQISLKEILLHYFRIINPTSKNKQGNDVGTQYRTGVYYTDDKDLEV INQVFDEVAKKYDQPLAVEKENLKNFVVAEDYHQDYLKKNPNGYCHINVNQAAYPVIDASKYPKPSDEE LKKTLSPEEYAVTQENQTERAFSNRYWDKFESGIYVDIATGEPLFSSKDKFESGCGWPSFTQPISPDVV TYKEDKSYNMTRMEVRSRVGDSHLGHVFTDGPQDKGGLRYCINSLSIRFIPKDQMEEKGYAYLLDYVD

SP110 nucleotide (SEQ ID NO:193)

TGTATAGTTTTTAGCGCTTGTTCTTCTAATTCTGNTAAAAATGAAGAAAATACTTCTAAAGAGCATGCG CCTGATAAAATAGTTTTAGATCATGCTTTCGGTCAAACTATATTAGATAAAAAACCTGAAAGAGTTGCA ACTATTGCTTGGGGAAATCATGATGTAGCATTAGCTTTAGGAATAGTTCCTGTTGGATTTTCAAAAGCA AATTACGGTGTAAGTGCTGATAAAGGAGTTTTACCATGGACAGAAGAAAAATCAAAGAACTAAATGGT $AAAGCTAACCTATTTGACGATTTGGATGGACTT\underline{AA}CTTTGAAGCAATATCAAATTCTAAACCAGATGTT$ ATCTTAGCAGGTTATTCTGGTATAACTAAAGAAGATTATGACACTCTATCA

SP110 amino acid (SEQ ID NO:194)

CIVFSACSSNSXKNEENTSKEHAPDKIVLDHAFGQTILDKKPERVATIAWGNHDVALALGIVPVGFSKA NYGVSADKGVLPWTEEKIKELNGKANLFDDLDGLNFEAISNSKPDVILAGYSGITKEDYDTLS

SP111 nucleotide (SEQ ID NO:195)

GTGTGTCGAGCATATTCTGAAGCAAACCTATCAAAATATAGAAATTATTTTAGTTGATGACGGTTCTAC GGATAATTCTGGGGAAATTTGTGATGCTTTTATGATGCAAGATAATCGTGTGCGAGTATTGCATCAAGA AAATAAGGGGGGGGCACAAGCTAAAAATATGGGGATTAGTGTAGCTAAGGGAGAGTACATCACGAT TGTTGATTCAGATGATATCGTAAAAGAAAATATGATTGAAACTCTTTATCAGCAAGTCCAAGAAAAAGGA TGCAGATGTTGTTATAGGGAATTACTATAATTATGACGAAAGTGACGGGAATTTTTATTTTTATGTAAC AGGGCAAGATTTTTGCGTCGAAGAATTAGCTATACAAGAAATTATGAACCGTCAAGCAGGAGATTGGAA ATTCAATAGCTCGGCCTTTATATTGCCGACATTTAAGTTGATTAAAAAAAGAATTATTCAATGAAGTTCA $\verb|CTTTTCAAATGGTCGCCGCTTTGATGATGAAGCAACTATGCATCGCTTTTATCTTTTAGCCTCTAAAAT| \\$ CGTCTTTATAAACGATAATCTCTATCTGTATAGAAGACGTTCAGGAAGCATCATGAGAACGGAATTTGA

TCTTTCCTGGGCAAGAGATATTGTTGAAGTGTTTTCTAAGAAAATATCGGATTGTCTTGGCTGGTTT GGATGTCTCCGTTCTGCGTATTCGATTTGTCAATCTTTTAAAAGATTATAAGCAAACTTTAGAATACCA TCAATTAACAGATACTGAGGAATATAAAGATATTTGTTTCAGATTAAAGTTGTTTTTTGATGCAGAACA AAGAAATGGTAAAAGT

88

SP111 amino acid (SEQ ID NO:196)

CYEHILKQTYQNIEIILVDDGSTDNSGEICDAFMMQDNRVRVLHQENKGGAAQAKNMGISVAKGEYITI VDSDDIVKENMIETLYQQVQEKDADVVIGNYYNYDESDGNFYFYVTGQDFCVEELAIQEIMNRQAGDWK FNSSAFILPTFKLIKKELFNEVHFSNGRRFDDEATMHRFYLLASKIVFINDNLYLYRRRSGSIMRTEFD LSWARDIVEVFSKKISDCVLAGLDVSVLRIRFVNLLKDYKQTLEYHQLTDTEEYKDICFRLKLFFDAEQ RNGKS

SP0112 nucleotide (SEQ ID NO:197)

SP0112 amino acid (SEQ ID NO:198)

CLDSIQNQTYQNFECLLINDGSPDHSSKICEEFVEKDSRFKYFEKANGGLSSARNLGİECSGGAYITFV DSDDWLEHDALDRLYGALKKENADISIGRYNSYDETRYVYMTYVTDPDDSLEVIEGKAIMDREGVEEVR NGNWTVAVLKLFKRELLQDLPFPIGKIAEDTYWTWKVLLRASRIVYLNRCVYWYRVGLSDTLSNTWSEK RMYDEIGAREEKIAILASSDYDLTNHILIYKNRLQRVIAKLEEQNMQFTEIYRRMMEKLSLLP

SP113 nucleotide (SEQ ID NO:199)

GTGCCTAGATAGTATTATTACTCAAACATATAAAAATATTGAGATTGTTGTCGTTAATGATGGTTCTAC GGATGCTTCAGGTGAAATTTGTAAAGAATTTTCAGAAATGGATCACCGAATTCTCTATATAGAACAAGA GGACTCGGATGATTGGATTGAGCAAGATTATGTAGAAACTCTATATAAAAAAATAGTAGAGTATCAGGC TGATATTGCAGTTGGTAATTATTCTTTCAACGAAAGTGAAGGAATGTTCTACTTTCATATATTGG AGACTCCTATTATGAGAAAGTATATGATAATGTTTCTATCTTTGAGAACTTGTATGAAACTCAAGAAAT GAAGAGTTTTGCTTTGATATCTGCTTGGGGTAAACTCTATAAGGCAAGATTGTTTGAGCAGTTGCGCTT $\verb|TTATTTAAATAAAAGTCTTTATGCTTATCGGATTAGAAAAGGTAGTTTATCAAGAGTTTGGACAGAAAA|$ $\tt GTGGATGCACGCTTTAGTTGATGCTATGTCTGAACGTATTACGCTACTAGCTAATATGGGTTATCCTCT$ $A GAGA \lambda A CACTTGGCAGTTTATCGTCAGATGTTGGAAGTCAGTCTCGCCAACGGTCAAGCTAGTGGTTT$ ATCTGACA'CAGCAACGTATAAAGAGTTTGAAATGAAACAAAGGCTTTTAAATCAGCTATCGAGACAAGA GGAAAGTGAAAAGAAAGCCATTGTCCTCGCAGCAAACTATGGCTATGTAGACCAAGTTTTAACGACAAT GATTAAGCAATTAAATAAGCGCTTAGAGAAGTTTGACTCAGAAATTATTAATTGTCGGGTAACTTCTGA ${\tt GCAAATTTCATGTTATAAATCGGATATTAGTTACACAGTCTTTTTACGCTATTTCATAGCTGATTTCGT}$ ${\tt GCAAGAAGACAAGGCCCTCTACTTGGACTGTGATCTAGTTGTAACGAAAAATCTGGATGACTTGTTTGC}$ TACAGACTTACAAGATTATCCTTTGGCTGCTGTTAGAGATTTTGGGGGGCAGAGCTTATTTTGGTCAAGA AATCTTTAATGCCGGTGTTCTCTTGGTAAACAATGCTTTTTGGAAAAAAAGAGAATATGACCCAAAAATT AATTGATGTAACCAATGAATGGCATGATAAGGTGGATCAGGCAGATCAGAGCATCTTGAATATGCTTTT TGAACATAAATGGTTGGAATTGGACTTTGATTATAATCATATTGTCATTAAACAGTTTGCTGATTA ${\tt TCAATTGCCTGAGGGTCAGGATTATCCTGCTATTATTCACTATCTTCTCATCGGAAACCGTGGAAAGA}$ ${\tt AAACCATCATTTACATCCATTACAAAGATCTCACATCTATCCAATAAAGGAACCTTTCACTTGTCTAAT}$ CTATACTGCCTCAGACCATATTGAACAAATTGAGACATTGGTTCAATCCTTGCCTGATATTCAGTTTAA WO 98/18930 PCT/US97/19422

Table 1

GATAGCAGCTAGAGTAATAGTTAGTGATCGATTGGCTCAGATGACAATTTATCCAAACGTGACTATATT
TAACGGAATTCACTATTTGGTAGATGTCGATAATGAATTGGTAGAAACCAGTCAAGTACTTTTAGATAT
TAATCATGGCGAAAAGACAGAAGAAATTCTCGATCAATTTGCTAATCTTGGCAAGCCTATCTTATCCTT
TGAAAATACTAAAACCTATGAAGTAGGTCAGGAGGCATATGCTGTTGACCAAGTTCAAGCAATGATTGA
AAAATTGAGAGAAATAAGCAAA

89

SP113 amino acid (SEQ ID NO:200)

CLDSIITQTYKNIEIVVVNDGSTDASGEICKEFSEMDHRILYIEQENAGLSAARNTGLNNMSGNYVTFV DSDDWIEQDYVETLYKKIVEYQADIAVGNYYSFNESEGMFYFHILGDSYYEKVYDNVSIFENLYETQEM KSFALISAWGKLYKARLFEQLRFDIGKLGEDGYLNQKVYLLSEKVIYLNKSLYAYRIRKGSLSRVWTEK WMHALVDAMSERITLLANMGYPLEKHLAVYRQMLEVSLANGQASGLSDTATYKEFEMKQRLLNQLSRQE ESEKKAIVLAANYGYVDQVLTTIKSICYHNRSIRFYLIHSDFPNEWIKQLNKRLEKFDSEIINCRVTSE QISCYKSDISYTVFLRYFIADFVQEDKALYLDCDLVVTKNLDDLFATDLQDYPLAAVRDFGGRAYFGQE IFNAGVLLVNNAFWKKENMTQKLIDVTNEWHDKVDQADQSILNMLFEHKWLELDFDYNHIVIHKQFADY QLPEGQDYPAIIHYLSHRKPWKDLAAQTYREVWWYYHGLEWTELGQNHHLHPLQRSHIYPIKEPFTCLI YTASDHIEQIETLVQSLPDIQFKIAARVIVSDRLAQMTIYPNVTIFNGIHYLVDVDNELVETSQVLLDI NHGEKTEEILDQFANLGKPILSFENTKTYEVGQEAYAVDQVQAMIEKLREISK

SP114 nucleotide (SEQ ID NO:201)

CATTCAGAAGCAGACCTATCAAAATCTGGAAATTATTCTTGTTGATGATGATGGTGCAACAGATGAAAGTGG
TCGCTTGTGTGATTCAATCGCTGAACAAGATGACAGGGTGTCAGTGCTTCATAAAAAAGAACGAAGGATT
GTCGCAAGCACGAAATGATGGGATGAAGCAGGCTCACGGGGATTATCTGATTTTTATTGACTCAGATGA
TTATATCCATCCAGAAATGATTCAGAGCTTATATGAGCAATTAGTTCAAGAAGATGCGGATGTTTCGAG
CTGTGGTGTCATGAATGTCTATAGCTAATGATGAAAGCCCACAGTCAGCCAATCAGGATGACTATTTTGT
CTGTGATTCTCAAACATTTCTAAAGGAATACCTCATAGGTGAAAAAATACCTGGGACGATTTGCAATAA
GCTAATCAAGAGACAGATTGCAACTGCCCTATCCTTTCCTAAGGGGTTGATTTACGAAGATGCCTATTA
CCATTTTGATTTAATCAAGTTGGCCAAGAAGTATGTGGTTAATACTAAACCCTATTATTACTATTTCCA
TAGAGGGGATAGTATTACGACCAAACCCTATGCAGAGAAGGATTTAGCCTATATTGATATCTACCAAAA
GTTTTTATATGAAGTTGTGAAAAACCTATCCTGACTTGAAAGAGGTCGCTTTTTTCAGATTGGCCTATGC
CCACTTCTTTATTCTGGATAAGATGTTGCTAGATGATCAGTATAAACAGTTTGAAGCCTATTCTCAGAT
TCATCGTTTTTTAAAAGGCCATGCCTTTGCTATTTCTAGGAATCCAATTTTCCGTAAGGGGAGAAGAT
TAGTGCTTTTGGCCCTATTCATAAATATTTCCTTATATCGATTCTTATTACTGAAAAAATTTGAAAAAATT

SP114 amino acid (SEQ ID NO:202)

IQKQTYQNLEIILVDDGATDESGRLCDSIAEQDDRVSVLHKKNEGLSQARNDGMKQAHGDYLIFIDSDD YIHPEMIQSLYEQLVQEDADVSSCGVMNVYANDESPQSANQDDYFVCDSQTFLKEYLIGEKIPGTICNK LIKRQIATALSFPKGLIYEDAYYHFDLIKLAKKYVVNTKPYYYYFHRGDSITTKPYAEKDLAYIDIYQK FYNEVVKNYPDLKEVAFFRLAYAHFFILDKMLLDDQYKQFEAYSQIHRFLKGHAFAISRNPIFRKGRRI SALALFINISLYRFLLKNIEKSKKLH

SP115 nucleotide (SEQ ID NO:203)

TAAGGCTGATAATCGTGTTCAAATGAGAACGACGATTAATAATGAATCGCCATTGTTGCTTTCTCCGTT GTATGGCAATGATAATGGTAACGGATTATGGTGGGGGAACACATTGAAGGGAGCATGGGAAGCTATTCC TGAAGATGTAAAGCCATATGCAGCGATTGAACTTCATCCTGCAAAAGTCTGTAAACCAACAAGTTGTAT TCCACGAGATACGAAAGAATTGAGAGAATGGTATGTCAAGATGTTGGAGGAAGCTCAAAGTCTAAACAT TCCAGTTTTCTTGGTTATTATGTCGGCTGGAGAGCGTAATACAGTTCCTCCAGAGTGGTTAGATGAACA AGCTCCGCATAGTGCTAAATATTTGGAAGTTTGTGCCAAATATGGAGCGCATTTTATCTGGCATGATCA TGAAAAATGGTTCTGGGAAACTATTATGAATGATCCGACATTCTTTGAAGCGAGTCAAAAATATCATAA AAATTTGGTGTTGGCAACTAAAAATACGCCAATAAGAGATGATGCGGGTACAGATTCTATCGTTAGTGG ATTTTGGTTGAGTGGCTTATGTGATAACTGGGGCTCATCAACAGATACATGGAAAATGGTGGGAAAAACA TTATACAAACACATTTGAAACTGGAAGAGCTAGGGATATGAGATCCTATGCATCGGAACCAGAATCAAT GATTGCTATGGAAATGAATGTATATACTGGGGGAGGCACAGTTTATAATTTCGAATGTGCCGCGTA TATACAAAATCCAGCTCCAAGTAAGGAAGAAGTTGTAAATAGAACAAAAGCTGTATTTTGGAATGGAGA AGGTAGGATTAGTTCATTAAACGGATTTTATCAAGGACTTTATTCGAATGATGAAACAATGCCTTTATA TAATAATGGGAGATATCATATTCTTCCTGTAATACATGAGAAAATTGATAAGGAAAAGATTTCATCTAT

SP115 amino acid (SEQ ID NO:204)

KADNRVQMRTTINNESPLLLSPLYGNDNGNGLWWGNTLKGAWEAIPEDVKPYAAIELHPAKVCKPTSCIPRDTKELREWYVKMLEEAQSLNIPVFLVIMSAGERNTVPPEWLDEQFQKYSVLKGVLNIENYWIYNNQLAPHSAKYLEVCAKYGAHFIWHDHEKWFWETIMNDPTFFEASQKYHKNLVLATKNTPIRDDAGTDSIVSGFWLSGLCDNWGSSTDTWKWWEKHYTNTFETGRARDMRSYASEPESMIAMEMMNVYTGGGTVYNFECAAYTFMTNDVPTPAFTKGIIPFFRHAIQNPAPSKEEVVNRTKAVFWNGEGRISSLNGFYQGLYSNDETMPLYNNGRYHILPVIHEKIDKEKISSIFPNAKILTKNSEELSSKVNYLNSLYPKLYEGDGYAQRVGNSWYIYNSNANINKNQQVMLPMYTNNTKSLSLDLTPHTYAVVKENPNNLHILLNNYRTDKTAMWALSGNFDASKSWKEELELANWISKNYSINPVDNDFRTTTLTLKGHTGHKPQINISGDKNHYTYTENWDENTHVYTITVNHNGMVEMSINTEGTGPVSFPTPDKFNDGNLNIAYAKPTTQSSVDYNGDPNRAVDGNRNGNFNSGSVTHTRADNPSWWEVDLKKMDKVGLVKIYNRTDAETQRLSNF

SP117 nucleotide (SEQ ID NO:205)

CTGTGGCAATCAGTCAGCTGCTTCCAAACAGTCAGCTTCAGGAACGATTGAGGTGATTTCACGAGAAAA
TGGCTCTGGGACACGGGGTGCCTTCACAGAAATCACAGGGATTCTCAAAAAAAGACGGTGATAAAAAAAT
TGACAACACTGCCAAAACAGCTGTGATTCAAAATAGTACAGAAGGTGTTCTCTCAGCAGTTCAAGGGAA
TGCTAATGCTATCGGCTACATCTCCTTGGGATCTTTAACGAAATCTGTCAAGGCTTTAGAGATTGATGG
TGTCAAGGCTAGTCGAGACACAGTTTTAGATGGTGAATACCCTCTTCAACGTCCCTTCAACATGTTTG
GTCTTCTAATCTTTCCAAGCTAGGTCAAGATTTTATCAGCTTTATCCACTCCAAACAAGGTCAACAAGT
GGTCACAGATAATAAATTTATTGAAGCTAAAACCGAAACCACGGAATATACAAGCCAACACTTATCAGG
CAAGTTGTCTGTTGTAGGTTCCACTTCAGTATCTTCTTTAATGGAAAAATTAGCAGAAGCTTATAAAAA
AGAAAATCCAGAAGTTACGATTGATATTACCTCTAATGGGTCTTCAGCAGGTATTACCGCTGTTAAGGA
GAAAACCGCTGATATTGGTATGGTTTCTAGGGAATTAACTCCTGAAGAAGGTAAGAGTCTCACCCATGA
TGCTATTGCTTTAGACGGTATTGCTGTTGTGGTCAATAATGACAATAAGGCAAGCCAAGTCAGTATGGC
TGAACTTGCAGACGTTTTTAGTGGCAAATTAACCACCTGGGACAAGATTAAA

SP117 amino acid (SEQ ID NO:206)

CGNQSAASKQSASGTIEVISRENGSGTRGAFTEITGILKKDGDKKIDNTAKTAVIQNSTEGVLSAVQGN ANAIGYISLGSLTKSVKALEIDGVKASRDTVLDGEYPLQRPFNIVWSSNLSKLGQDFISFIHSKQGQQV VTDNKFIEAKTETTEYTSQHLSGKLSVVGSTSVSSLMEKLAEAYKKENPEVTIDITSNGSSAGITAVKE KTADIGMVSRELTPEEGKSLTHDAIALDGIAVVVNNDNKASQVSMAELADVFSGKLTTWDKIK

SP118 nucleotide (SEQ ID NO:207)

TTGTCAACAACAACATGCTACTTCTGAGGGGACGAATCAAAGGCAAAGCAGTTCAGCGAAAGTTCCATG
GAAAGCTTCATACACCAACCTAAACAACCAGGTAAGTACAGAAGAGAGTCAAATCTCTCTTATCAGCTCA
CTTGGATCCAAATAGTGTTGATGCATTTTTTTAATCTCGTTAATGACTATAATACCATTGTCGGCTCAAC
TGGCTTATCAGGAGATTTCACTTCCTTTACTCACACCGAATACGATGTTGAGAAAATCAGTCATCTCTG
GAATCAAAAGAAGGAGGCGATTTTGTTGGGACCAACTGCCGTATCAATAGTTATTGTCTTTTTGAAAAATTC
AGTCACCATTCCAAAGCTTGAAAAGAATGACCAGTTGCTTTTCCTAGATAATGATGCGATTGATAAAGG
AAAGGTCTTTGATTCACAAGATAAGGAAGAGTTTGATATTCTATTTTCGAGAGTTCCAACTGAGTCAAC
TACAGATGTCAAGGTTCACGCTGAAAAGATGGAAGCATTCTTCTCACAATTTCAATTCAATTCAATAGAAAAAGC
TCGAATGCTGTCTGTAGTCTTGCACGACAATTTGGATGAGAAATTGACTTTCGAAGAGCCCCTACCAAGCGAT

 ${\tt TAAATTTGCTAGTAAGGAAGATTGCTACAAGTATTTGGGCACCAAGTATGCGGATTATACAGGCGAGGGACTAAGCCTTAAGCCTTTTATCATGGATAATGATAAGTGGGTTAAACTT}$

91

SP118 amino acid (SEQ ID NO:208)

CQQQHATSEGTNQRQSSSAKVPWKASYTNLNNQVSTEEVKSLLSAHLDPNSVDAFFNLVNDYNTIVGST GLSGDFTSFTHTEYDVEKISHLWNQKKGDFVGTNCRINSYCLLKNSVTIPKLEKNDQLLFLDNDAIDKG KVFDSQDKEEFDILFSRVPTESTTDVKVHAEKMEAFFSQFQFNEKARMLSVVLHDNLDGEYLFVGHVGV LVPADDGFLFVEKLTFEEPYQAIKFASKEDCYKYLGTKYADYTGEGLAKPFIMDNDKWVKL

SP119 nucleotide (SEQ ID NO:209)

SP119 amino acid (SEQ ID NO:210)

CSGKSVTSEHQTKDEMKTEQTASKTSAAKGKEVADFELMGVDGKTYRLSDYKGKKVYLKFWASWCSICL ASLPDTDEIAKEAGDDYVVLTVVSPGHKGEQSEADFKNWYKGLDYKNLPVLVDPSGKLLETYGVRSYPT OAFIDKEGKLVKTHPGFMEKDAILQTLKELA

SP120 nucleotide (SEQ ID NO:211)

SP120 amino acid (SEQ ID NO:212)

SQIEKAAVSQGGKAVKKTEISKDADLHEIYLAGGCFWGVEEYFSRVPGVTDAVSGYANGRGETTKYELI NQTGHAETVHVTYDAKQISLKEILLHYFRIINPTSKNKQGNDVGTQYRTGVYYTDDKDLEVINQVFDEV AKKYDQPLAVEKENLKNFVVAEDYHQDYLKKNPNGYCHINVNQAAYPVIDASKYPKPSDEELKKTLSPE EYAVTQENQTERAFSNRYWDKFESGIYVDIATGEPLFSSKDKFESGCGWPSFTQPISPDVVTYKEDKSY NMTRMEVRSRVGDSHLGHVFTDGPQDKGGLRYCINSLSIRFIPKDQMEEKGTLIY

SP121 nucleotide (SEQ ID NO:213)

Α

TTATGCTGCTAAAAACGCTGGCTTAGCTGTCGCAACTGTCAGCTTGAAGATGAAGGACGGCGACGCCAA

SP121 amino acid (SEQ ID NO:214) CQSGSNGSQSAVDAIKQKGKLVVATSPDYAPFEFQSLVDGKNQVVGADIDMAQAIADELGVKLEISSMS FDNVLTSLQTGKADLAVAGISATDERKEVFDFSIPYYENKISFLVRKADVEKYKDLTSLESANIAAQKG TVPESMVKEQLPKVQLTSLTNMGEAVNELQAGKIDAVHMDEPVALSYAAKNAGLAVATVSLKMKDGDAN

SP122 nucleotide (SEQ ID NO:215)

GGAAACTTCACAGGATTTTAAAGAGAAGAAAACAGCAGTCATTAAGGAAAAAGAAGTTGTTAGTAAAAA TCCTGTGATAGACAATAACACTAGCAATGAAGAAGCAAAAAATCAAAGAAGAAAATTCCAATAAATCCCA AGGAGATTATACGGACTCATTTGTGAATAAAAACACAGAAAATCCCAAAAAAGAAGATAAAGTTGTCTA TATTGCTGAATTTAAAGATAAGAATCTGGAGAAAAAGCAATCAAGGAACTATCCAGTCTTAAGAATAC AAAAGTTTTATATACTTATGATAGAATTTTTAACGGTAGTGCCATAGAAACAACTCCAGATAACTTGGA CAAAATTAAACAAATAGAAGGTATTTCATCGGTTGAAAGGGCACAAAAAGTCCAACCCATGATGAATCA TGCCAGAAAGGAAATTGGAGTTGAGGAAGCTATTGATTACCTAAAGTCTATCAATGCTCCGTTTGGGAA AAATTTTGATGGTAGAGGTATGGTCATTTCAAATATCGATACTGGAACAGATTATAGACATAAGGCTAT GAGAATCGATGATGATGCCAAAGCCTCAATGAGATTTAAAAAAGAAGACTTAAAAAGGCACTGATAAAAA TTATTGGTTGAGTGATAAAATCCCTCATGCGTTCAATTATTATAATGGTGGCAAAATCACTGTAGAAAA ATATGATGATGGAAGGGATTATTTTGACCCACATGGGATGCATATTGCAGGGATTCTTGCTGGAAATGA TACTGAACAAGACATCAAAAACTTTAACGGCATAGATGGAATTGCACCTAATGCACAAATTTTCTCTTA CAAAATGTATTCTGACGCAGGATCTGGGTTTGCGGGTGATGAAACAATGTTTCATGCTATTGAAGATTC TATCAAACACAACGTTGATGTTTCGGTATCATCTGGTTTTACAGGAACAGGTCTTGTAGGTGAGAA ATATTGGCAAGCTATTCGGGCATTAAGAAAAGCAGGCATTCCAATGGTTGTCGCTACGGGTAACTATGC GACTTCTGCTTCAAGTTCTTCATGGGATTTAGTAGCAAATAATCATCTGAAAATGACCGACACTGGAAA TGTAACACGAACTGCAGCACATGAAGATGCGATAGCGGTCGCTTCTGCTAAAAATCAAACAGTTGAGTT TGATAAAGTTAACATAGGTGGAGAAAGTTTTAAATACAGAAATATAGGGGCCTTTTTCGATAAGAGTAA AGACCAAGATTTGATAGGTTTGGATCTTAGGGGCAAAATTGCAGTAATGGATAGAATTTATACAAAGGA TTTAAAAAATGCTTTTAAAAAAGCTATGGATAAGGGTGCACGCGCCATTATGGTTGTAAATACTGTAAA TTACTACAATAGAGATAATTGGACAGAGCTTCCAGCTATGGGATATGAAGCGGATGAAGGTACTAAAAG TGAAGTCAAAAGAAATAATAAAGAAGATTTTAAAGATAAATTGGAGCAATACTATCCAATTGATATGGA AAGTTTTAATTCCAACAAACCGAATGTAGGTGACGAAAAAGAGATTGACTTTAAGTTTGCACCTGACAC AGACAAAGAACTCTATAAAGAAGATATCATCGTTCCAGCAGGATCTACATCTTGGGGGCCAAGAATAGA TTTACTTTTAAAACCCGATGTTTCAGCACCTGGTAAAAATATTAAATCCACGCTTAATGTTATTAATGG CAAATCAACTTATGGCTATATGTCAGGAACTAGTATGGCGACTCCAATCGTGGCAGCTTCTACTGTTTT GATTAGACCGAAATTAAAGGAAATGCTTGAAAGACCTGTATTGAAAAATCTTAAGGGAGATGACAAAAT TTTGAGAAATGAAGTTGTAGCAACTTTCAAAAACACTGATTCTAAAGGTTTGGTAAACTCATATGGTTC CATTTCTCTTAAAGAATAAAAGGTGATAAAAAATACTTTACAATCAAGCTTCACAATACATCAAACAG ACCTTTGACTTTTAAAGTTTCAGCATCAGCGATAACTACAGATTCTCTAACTGACAGATTAAAACTTGA TGAAACATATAAAGATGAAAAATCTCCAGATGGTAAGCAAATTGTTCCAGAAATTCACCCAGAAAAAGT CAAAGGAGCAAATATCACATTTGAGCATGATACTTTCACTATAGGCGCAAATTCTAGCTTTGATTTGAA AGTGGAAGCGATGGAAGCTCTAAACTCCAGCGGGAAGAAAATAAACTTCCAACCTTCTTTGTCGATGCC TCTAATGGGATTTGCTGGGAATTGGAACCACGAACCAATCCTTGATAAATGGGCTTGGGAAGAAGGGTC AAGATCAAAAACACTGGGAGGTTATGATGATGATGGTAAACCGAAAATTCCAGGAACCTTAAATAAGGG AATTGGTGGAGAACATGGTATAGATAAATTTAATCCAGCAGGAGTTATACAAAATAGAAAAGATAAAAA TACAACATCCCTGGATCAAAATCCAGAATTATTTGCTTTCAATAACGAAGGGATCAACGCTCCATCATC AAGTGGTTCTAAGATTGCTAACATTTATCCTTTAGATTCAAATGGAAATCCTCAAGATGCTCAACTTGA

SP122 amino acid (SEQ ID NO:216)

ETSQDFKEKKTAVIKEKEVVSKNPVIDNNTSNEEAKIKEENSNKSQGDYTDSFVNKNTENPKKEDKVVY IAEFKDKESGEKAIKELSSLKNTKVLYTYDRIFNGSAIETTPDNLDKIKQIEGISSVERAQKVQPMMNH

ARKEIGVEEAIDYLKSINAPFGKNFDGRGMVISNIDTGTDYRHKAMRIDDDAKASMRFKKEDLKGTDKN YWLSDKIPHAFNYYNGGKITVEKYDDGRDYFDPHGMHIAGILAGNDTEQDIKNFNGIDGIAPNAQIFSY KMYSDAGSGFAGDETMFHAIEDSIKHNVDVVSVSSGFTGTGLVGEKYWQAIRALRKAGIPMVVATGNYA TSASSSSWDLVANNHLKMTDTGNVTRTAAHEDAIAVASAKNQTVEFDKVNIGGESFKYRNIGAFFDKSK ITTNEDGTKAPSKLKFVYIGKGQDQDLIGLDLRGKIAVMDRIYTKDLKNAFKKAMDKGARAIMVVNTVN YYNRDNWTELPAMGYEADEGTKSQVFSISGDDGVKLWNMINPDKKTEVKRNNKEDFKDKLEQYYPIDME SFNSNKPNVGDEKEIDFKFAPDTDKELYKEDIIVPAGSTSWGPRIDLLLKPDVSAPGKNIKSTLNVING KSTYGYMSGTSMATPIVAASTVLIRPKLKEMLERPVLKNLKGDDKIDLTSLTKIALQNTARPMMDATSW KEKSQYFASPRQQGAGLINVANALRNEVVATFKNTDSKGLVNSYGSISLKEIKGDKKYFTIKLHNTSNR PLTFKVSASAITTDSLTDRLKLDETYKDEKSPDGKQIVPEIHPEKVKGANITFEHDTFTIGANSSFDLN AVINVGEAKNKNKFVESFIHFESVEAMEALNSSGKKINFQPSLSMPLMGFAGNWNHEPILDKWAWEEGS RSKTLGGYDDDGKPKIPGTLNKGIGGEHGIDKFNPAGVIQNRKDKNTTSLDQNPELFAFNNEGINAPSS SGSKIANIYPLDSNGNPQDAQLERGLTPSPLVLRSAEEGLI

SP123 nucleotide (SEQ ID NO:217)

TGTGGTCGAAGTTGAGACTCCTCAATCAATAACAAATCAGGAGCAAGCTAGGACAGAAAACCAAGTAGT AGAGACAGAGGAAGCTCCAAAAGAAGAAGCACCTAAAACAGAAGAAGTCCAAAGGAAGAACCAAAATC GGAGGTAAAACCTACTGACGACACCCTTCCTAAAGTAGAAGAGGGGGAAAGAAGATTCAGCAGAACCAGC TCCAGTTGAAGAAGTAGGTGGAGAAGTTGAGTCAAAACCAGAGGAAAAAGTAGCAGTTAAGCCAGAAAG TCAACCATCAGACAAACCAGCTGAGGAATCAAAAGTTGAACAAGCAGGTGAACCAGTCGCGCCAAGAGA AGACGAAAAGGCACCAGTCGAGCCAGAAAAGCAACCAGAAGCTCCTGAAGAAGAGAAGGCTGTAGAGGA AACACCGAAACAAGAAGAGTCAACTCCAGATACCAAGGCTGAAGAAACTGTAGAACCAAAAGAGGAGAC GGAACCAAAAGTTGAACAAGCAGGTGAACCAGTCGCGCCAAGAGAAGACGAACAGGCACCAACGGCACC AGTTGAGCCAGAAAAGCAACCAGAAGTTCCTGAAGAAGAGAGGGCTGTAGAGGAAACACCGAAACCAGA AGATAAAATAAAGGGTATTGGTACTAAAGAACCAGTTGATAAAAGTGAGTTAAATAATCAAATTGATAA AGCTAGTTCAGTTTCTCCTACTGATTATTCTACAGCAAGTTACAATGCTCTTGGACCTGTTTTAGAAAC TGCAAAAGGTGTCTATGCTTCAGAGCCTGTAAAACAGCCTGAGGTAAATAGCGAGACAAATAAACTTAA AACGGCTATTGACGCTCTAAACGTTGATAAAACTGAATTAAACAATACGATTGCAGATGCAAAAACAAA GGTAAAAGAACATTACAGTGATAGAAGTTGGCAAAACCTCCAAACTGAAGTTACAAAGGCTGAAAAAAGT TGCAGCTAATACAGATGCTAAACAAAGTGAAGTTAACGAAGCTGTTGAAAAATTAACTGCAACTATTGA AAAATTGGTTGAATTATCTGAAAAGCCAATATTAACATTGACTAGTACCGATAAGAAAATATTGGAACG GAAAAAAGGAGAAGAAGTTATTAATACTGTAGTCCTTACAGATGACAAGGTAACAACAGAAACTATAAG CGCTGCATTTAAGAACCTAGAGTACTACAAAGAATACACCCTATCTACAACTATGATTTACGACAGAGG TAACGGTGAAGAAACTGAAACTCTAGAAAATCAAAATATTCAATTAGATCTTAAAAAAGTTGAGCTTAA AAATATTAAACGTACAGATTTAATCAAATACGAAAATGGAAAAGAAACTAATGAATCACTGATAACAAC TATTCCTGATGATAAGAGCAATTATTATTTAAAAAATAACTTCAAATAATCAGAAAAACTACATTACTAGC TGTTAAAAATATAGAAGAAACTACGGTTAACGGAACACCTGTATATAAAGTTACAGCAATCGCAGACAA TTTAGTCTCTAGAACTGCTGATAATAAATTTGAAGAAGAA

SP123 amino acid (SEQ ID NO:218)

VVEVETPQSITNQEQARTENQVVETEEAPKEEAPKTEESPKEEPKSEVKPTDDTLPKVEEGKEDSAEPA
PVEEVGGEVESKPEEKVAVKPESQPSDKPAEESKVEQAGEPVAPREDEKAPVEPEKQPEAPEEEKAVEE
TPKQEESTPDTKAEETVEPKEETVNQSIEQPKVETPAVEKQTEPTEEPKVEQAGEPVAPREDEQAPTAP
VEPEKQPEVPEEEKAVEETPKPEDKIKGIGTKEPVDKSELNNQIDKASSVSPTDYSTASYNALGPVLET
AKGVYASEPVKQPEVNSETNKLKTAIDALNVDKTELNNTIADAKTKVKEHYSDRSWQNLQTEVTKAEKV
AANTDAKQSEVNEAVEKLTATIEKLVELSEKPILTLTSTDKKILEREAVAKYTLENQNKTKIKSITAEL
KKGEEVINTVVLTDDKVTTETISAAFKNLEYYKEYTLSTTMIYDRGNGEETETLENQNIQLDLKKVELK
NIKRTDLIKYENGKETNESLITTIPDDKSNYYLKITSNNQKTTLLAVKNIEETTVNGTPVYKVTAIADN
LVSRTADNKFEEE

SP124 amino acid (SEQ ID NO:219)

GAATTTTGAAAATGTAGAGATAGAACGTTCTGGTCAAGATAATATTGCATCATTAGCCAATACTATGAA AGGTTCTTCAGTTATTACAAATGTCAAAATTACAGGCACACTTTCAGGTCGTAATAATGTTGCTGGATT TGGAAATGGCTCTCATACAGGGGGAATTGCAGGTACAAACTATAGAGGAATTGTTAGAAAAAGCATATGT TGATGCTACTATTACAGGAAACAAAACACGCGCCAGCTTGTTAGTTCCTAAAGTAGATTATGGATTAAC TCTAGACCATCTTATTGGTACAAAAGCTCTCCTAACTGAGTCGGTTGTAAAAGGTAAAATAGATGTTTC CTATGCTAAGATTATCCGTGGAGAGGAGTTATTCGGCTCTAACGACGTTGATGATTCTGATTATGCTAG TGCTCATATAAAAGATTTATATGCGGTAGAGGGATATTCGTCAGGTAATAGATCATTTAGGAAATCTAA AACATTTACTAAATTAACTAAAGAACAAGCTGATGCTAAAGTTACTACTTTCAATATTACTGCTGATAA ATTAGAAAGTGATCTATCTCCTCTTGCAAAACTTAATGAAGAAAAAGCCTATTCTAGTATTCAAGATTA TAACGCTGAATATAACCAAGCCTATAAAAATCTTGAAAAATTAATACCATTCTACAATAAAGATTATAT GATGAACAACAATGAGTTTATCACAAACCTAGATGAAGCTAATAAAATTATTGTTCACTATGCGGACGG TACAAAAGATTACTTTAACTTGTCTTCTAGCAGTGAAGGTTTAAGTAATGTAAAAGAATATACTATAAC TGACTTAGGAATTAAATATACACCTAATATCGTTCAAAAAGATAACACTACTCTTGTTAATGATATAAA ATCTATTTTAGAATCAGTAGAGCTTCAGTCTCAAACGATGTATCAGCATCTAAATCGATTAGGTGACTA TAGAGTTAATGCAATCAAAGATTTATATTTAGAAGAAAGCTTCACAGATGTTAAAGAAAACTTAACAAA CCTAATCACAAAATTAGTTCAAAACGAAGAACATCAACTAAATGATTCTCCAGCTGCTCGTCAAATGAT

 ${\tt TCGTGATAAAGTCGAGAAAAACAAAGCAGCTTTATTACTAGGTTTAACTTACCTAAATCGTTACTATGG}$ ${\tt AGTTAAATTTGGTGATGTTAATATTAAAGAATTAATGCTATTCAAACCAGATTTCTATGGTGAAAAAGT}$ ${\tt TAGCGTATTAGACAGATTAATTGAAATCGGTTCTAAAGAGACACATTAAAGGTTCACGTACATTCGA}$

SP124 amino acid (SEQ ID NO:220)

CGCATTCGGTCAAGTA

TPVYKVTAIADNLVSRTADNKFEEEYVHYIEKPKVHEDNVYYNFKELVEAIQNDPSKEYRLGQSMSARN VVPNGKSYITKEFTGKLLSSEGKQFAITELEHPLFNVITNATINNVNFENVEIERSGQDNIASLANTMK GSSVITNVKITGTLSGRNNVAGFVNNMNDGTRIENVAFFGKLHSTSGNGSHTGGIAGTNYRGIVRKAYV DATITGNKTRASLLVPKVDYGLTLDHLIGTKALLTESVVKGKIDVSNPVEVGAIASKTWPVGTVSNSVS YAKIIRGEELFGSNDVDDSDYASAHIKDLYAVEGYSSGNRSFRKSKTFTKLTKEQADAKVTTFNITADK LESDLSPLAKLNEEKAYSSIQDYNAEYNQAYKNLEKLIPFYNKDYIVYQGNKLNKEHHLNTKEVLSVTA MNNNEFITNLDEANKIIVHYADGTKDYFNLSSSSEGLSNVKEYTITDLGIKYTPNIVQKDNTTLVNDIK SILESVELQSQTMYQHLNRLGDYRVNAIKDLYLEESFTDVKENLTNLITKLVQNEEHQLNDSPAARQMI RDKVEKNKAALLLGLTYLNRYYGVKFGDVNIKELMLFKPDFYGEKVSVLDRLIEIGSKENNIKGSRTFD AFGQV

SP125 nucleotide (SEQ ID NO:221)

ATTAGACAGATTAATTGAAATCGGTTCTAAAGAGAACAACATTAAAGGTTCACGTACATTCGACGCATT CGGTCAAGTATTGGCTAAATATACTAAATCAGGTAATTTAGATGCATTTTTAAATTATAATAGACAATT GTTCACAAATATAGACAATÁTGAACGATTGGTTTATTGATGCTACAGAAGACCATGTCTACATCGCAGA ACGCGCTTCTGAGGTCGAAGAAATTAAAAATTCTAAACATCGTGCATTCGATAATTTAAAAACGAAGTCA TGCAATTGCCTTTGGTAGTGCAGAGCGATTAGGTAAAAAATCATTAGAAGATATTAAAGATATCGTTAA CAAAGCTGCAGATGGTTATAGAAACTATTATGATTTCTGGTATCGTCTAGCGTCTGATAACGTTAAACA ACGACTACTAAGAGATGCTGTTATTCCTATTTGGGAAGGTTATAACGCTCCTGGTGGATGGGTTGAAAA ATATGGCCGCTATAATACCGACAAAGTATATACTCCTCTTAGAGAATTCTTTGGTCCTATGGATAAGTA TTATAATTATAATGGAACAGGAGCTTATGCTGCTATATATCCTAACTCTGATGATATTAGAACTGATGT AAAATATGTTCATTTAGAAATGGTTGGTGAATACGGTATTTCAGTTTACACACATGAAACAACACACGT CAACGACCGTGCGATTTACTTAGGTGGCTTTGGACACCGTGAAGGTACTGATGCTGAAGCATATGCTCA ${\tt GGGTATGCTACAAACTCCTGTTACTGGTAGTGGATTTGATGAGTTTGGTTCTTTAGGTATTAATATGGT}$ ATTTAAACGCAAAAATGATGGGAATCAGTGGTATATTACAGATCCAAAAACTCTAAAAAACACGAGAAGA TATTAATAGATATATGAAGGGTTATAATGACACTTTAACTCTTCTTGATGAAATTGAGGCTGAATCTGT CAATAAATTAAATCAATGGGATAAAATTCGAAATCTAAGTCAAGAAGAGAAAAATGAATTAAATATTCA ATCTGTTAATGATTTAGTTGATCAACAATTAATGACTAATCGCAATCCAGGTAATGGTATCTATAAACC CGAAGCAATTAGCTATAACGATCAATCACCTTATGTAGGTGTTAGAATGATGACCGGTATCTACGGAGG TAATACTAGTAAAGGTGCTCCTGGAGCTGTTTCATTCAAACATAATGCTTTTAGATTATGGGGTTACTA Table 1 95

SP125 amino acid (SEQ ID NO:222)

LDRLIEIGSKENNIKGSRTFDAFGQVLAKYTKSGNLDAFLNYNRQLFTNIDNMNDWFIDATEDHVYIAE RASEVEEIKNSKHRAFDNLKRSHLRNTILPLLNIDKAHLYLISNYNAIAFGSAERLGKKSLEDIKDIVN KAADGYRNYYDFWYRLASDNVKQRLLRDAVIPIWEGYNAPGGWVEKYGRYNTDKVYTPLREFFGPMDKY YNYNGTGAYAAIYPNSDDIRTDVKYVHLEMVGEYGISVYTHETTHVNDRAIYLGGFGHREGTDAEAYAQ GMLQTPVTGSGFDEFGSLGINMVFKRKNDGNQWYITDPKTLKTREDINRYMKGYNDTLTLLDEIEAESV ISQQNKDLNSAWFKKIDREYRDNNKLNQWDKIRNLSQEEKNELNIQSVNDLVDQQLMTNRNPGNGIYKP EAISYNDQSPYVGVRMMTGIYGGNTSKGAPGAVSFKHNAFRLWGYYGYENGFLGYASNKYKQQSKTDGE SVLSDEYIIKKISNNTFNTIEEFKKAYFKEVKDKATKGLTTFEVNGSSVSSYDDLLTLFKEAVKKDAET LKQEANGNKTVSMNNTVKLKEAVYKKLLQQTNSFKTSIFK

SP126 nucleotide (SEQ ID NO:223)

SP126 amino acid (SEQ ID NO:224)

KTDERSKVFDFSIPYYTAKNKLIVKKSDLTTYQSVNDLAQKKVGAQKGSIQETMAKDLLQNSSLVSLPK NGNLITDLKSGQVDAVIFEEPVSKGFVENNPDLAIADLNFEKEQDDSYAVAMKKDSKKLKRQFDKTIQK LKESGELDKLIEEAL

SP127 nucleotide (SEQ ID NO:225)

SP127 amino acid (SEQ ID NO:226)

CENQATPKETSAQKTIVLATAGDVPPFDYEDKGNLTGFDIEVLKAVDEKLSDYEIQFQRTAWESIFPGL DSGHYQAAANNLSYTKERAEKYLYSLPISNNPLVLVSNKKNPLTSLDQIAGKTTQEDTGTSNAQFINNW NQKHTDNPATINFSGEDIGKRILDLANGEFDFLVFDKVSVQKIIKDRGLDLSVVDLPSADSPSNYIIFS SDQKEFKEQFDKALKELYQDGTLEKLSNTYLGGSYLPDQSQLQ

Table 2 S. pneumoniae Antigenic Epitopes

SP001

Lys-1 to Ile-10; Leu-13 to Lys-32; Arg-41 to Ile-51; Ser-85 to Glu-97; Ala-159 to His-168; Val-309 to Thr-318; Val-341 to Asn-352; Asn-415 to Met-430; Phe-454 to Asn-464; Ser-573 to Gly-591; Asn-597 to Thr-641; and Asn-644 to Ala-664.

SP004

Thr-9 to Thr-24; Ile-29 to Ala-48; Thr-49 to Val-56; Val-286 to Val-312:

Pro-316 to Glu-344; Val-345 to Ile-367; Gln-368 to Val-399; Ser-400 to Glu-431; Asn-436 to Ala-457; Ile-467 to Ala-498; and Thr-499 to Glu-

SP006

Glu-1 to Lys-13; Pro-24 to Gly-36; Val-104 to Thr-112; Ala-118 to Asn-130; Trp-137 to Ala-146; Ser-151 to Ile-159; Ile-181 to Leu-188; and Pro-194 to Tyr-202.

SP007

Gly-1 to Asn-7; Tyr-24 to Gln-34; His-47 to Phe-55; Ser-60 to Ala-67; Ala-122 to Leu-129; Leu-221 to Lys-230; Val-236 to Phe-256; and Asp-271 to Gly-283; and Leu-291 to Asp-297.

SP008

Leu-4 to Lys-17; Gln-24 to Leu-32; Asp-60 to Ser-66; Ser-70 to Asp-76; Ala-276 to Lys-283; Asn-304 to Lys-311; and Thr-429 to Pro-437.

SP009

Thr-4 to Glu-11; Leu-50 to Asp-60; Ile-102 to Trp-123; and Ser-138 to Ile-157.

SP010

Phe-34 to Gly-41; Asp-44 to Lys-50; Leu-172 to Val-186; Leu-191 to Val-198; Ser-202 to Ile-209; and Val-213 to Leu-221.

Asn-2 to Thr-10; Asp-87 to Ala-102; Tyr-125 to Glu-132; Thr-181 to Tyr-189; Arg-217 to Thr-232; Asn-257 to Lys-264; Pro-271 to Ser-278; Tyr-317 to Ala-325; Glu-327 to Pro-337; and Thr-374 to Val-381.

SP012

Gly-1 to Lys-19; Phe-34 to Tyr-41; Leu-109 to Lys-126; and Leu-231 to Glu-247.

SP013

Ala-1 to Lys-12; Ile-42 to Pro-53; Leu-138 to Lys-146; Ile-205 to Lys-217; Ser-235 to Ile-251; and Ser-261 to Tyr-272.

SP014

Gly-1 to Val-16; Leu-35 to Leu-44; Asp-73 to Asp-81; Ile-83 to Asp-92; Glu-145 to Ile-153; Phe-188 to Asn-196; Ser-208 to Phe-215; Ile-224 to Leu-231; and Asn-235 to Ala-243.

SP015

Ser-1 to Pro-16; Asn-78 to Glu-88; Ala-100 to Val-108; Ala-122 to Thr-129; Thr-131 to Ser-137; Leu-201 to Ser-220; and Gly-242 to Val-251.

WO 98/18930 PCT/US97/19422

Table 2

97

S. pneumoniae Antigenic Epitopes

SP016

Gly-1 to Glu-20; Thr-30 to Val-38; Gln-94 to Asn-105; Lys-173 to Pro-182; Gly-189 to Arg-197; Ser-207 to Val-224; Pro-288 to Leu-298; Ala-327 to Ala-342; and Ser-391 to Ala-402.

SP017

Ser-1 to Thr-12; Ala-36 to Tyr-45; Gln-48 to Ile-54; Lys-59 to Lys-76; Tyr-113 to Leu-138; and Phe-212 to Asp-219.

Val-97 to Glu-117; Asp-163 to Leu-169; Thr-182 to Thr-191; and Lys-241 to Ser-250.

Asn-18 to Lys-25; Thr-47 to Glu-60; Trp-75 to Val-84; Gly-102 to Val-110; Pro-122 to Ala-131; and Glu-250 to Pro-258.

Ser1 to Asp-8; Val-44 to Asp-54; Ala-117 to Val-125; Thr-165 to Thr-173: and Glu-180 to Pro-189.

SP022

Phe-5 to Lys-13; Thr-20 to Ser-36; Glu-59 to Lys-81; Tyr-85 to Gly-93; Trp-94 to Trp-101; and Thr-195 to Trp-208.

SP023

Gln-45 to Glu-59; Asp-69 to Pro-85; Lys-111 to Asn-121; Pro-218 to Ala-228; and Glu-250 to Asn-281.

Gln-14 to Thr-20; Gly-27 to Phe-33; Gly-63 to Glu-71; and Ile-93 to Phe-102.

Asp-171 to Pro-179; Tyr-340 to Glu-350; Pro-455 to Tyr-463; and Asp-474 to Pro-480.

SP030

Leu-22 to Leu-37; Trp-81 to Ala-90; Phe-101 to Ala-106; Thr-124 to Tyr-130; and Asn-138 to Glu-144.

SP031

Asp-8 to Val-16; Gly-27 to Thr-35; Gly-178 to Asp-195; Thr-200 to Asp209; Trp-218 to Leu-224; and Lys-226 to Asp-241.

SP032

Ser-9 to Asp-28; Phe-31 to Val-40; Gly-42 to Arg-50; Ile-52 to Leu-60; Asp-174 to Phe-186; Leu-324 to Met-333; and Thr-340 to Asn-347.

Gln-2 to Ile-13; Phe-46 to Ile-53; and Asp-104 to Thr-121.

SP034

Glu-36 to Gly-43; Ala-188 to Asp-196; Trp-313 to Gly-320; and Leu-323 to Leu-329.

电流性 医腺性性病 化二苯基

Table 2 S. pneumoniae Antigenic Epitopes

SP035

Arg-19 to Asp-36; Asp-47 to Val-57; Asn-134 to Thr-143; Asp-187 to Arg-196; and Glu-222 to Ser-230.

SP036

Arg-10 to Arg-17; Lys-29 to Ser-39; Ser-140 to Ala-153; Arg-158 to Tyr-169; Asp-175 to Ala-183; Gly-216 to Asn-236; Ala-261 to Leu-270; Arg-282 to Phe-291; and Thr-297 to Ala-305; Pro-342 to Gln-362; Phe-455 to Asp-463; His-497 to Thr-511; Ala-521 to Gly-529; Ile-537 to Val-546; Ile-556 to Ala-568; Pro-581 to Ser-595; Glu-670 to Ala-685; Ser-696 to Ala-705 and Leu-782 to Ser-791.

SP038

Glu-61 to Pro-69; Phe-107 to Ala-115; Leu-130 to Tyr-141; Ala-229 to Glu-237; Ser-282 to Asn-287; Ala-330 to Glu-338; and Tyr-387 to Glu-393.

SP039

Ser-28 to Asp-35; Pro-88 to Pro-96; Leu-125 to Arg-135; Phe-149 to Leu-157; Gln-246 to Val-254; Ala-357 to Thr-362; Gly-402 to Lys-411; and Leu-440 to Pro-448.

Thr-21 to Ile-30; His-54 to Gln-68; Arg-103 to Leu-117; and Thr-127 to Leu-136.

SP041

Gly-36 to Asp-49; Leu-121 to Val-128; and Ala-186 to Ile-196.

SP042

Gly-11 to Arg-19; Ile-23 to Lys-31; His-145 to Asn-151; Gln-159 to Asp-166; Ile-175 to Asp-181; Gly-213 to Tyr-225; Ile-283 to Val-291; Pro-329 to Glu-364; Arg-372 to Ser-386; Thr-421 to Phe-430; Leu-445 to Val-453; Ile-486 to Ala-497; Asp-524 to Ala-535; His-662 to Gly-674; and His-679 to Gln-702.

SP043

Lys-2 to Asp-12; Val-58 to Asn-68; Ser-87 to Asp-95; and Asp-102 to Lys-117.

Gln-3 to Lys-11; Asp-37 to Tyr-52; Glu-171 to Leu-191; His-234 to Asn-247; and Asn-283 to Ala-291.

SP045

Tyr-52 to Ile-63; Asp-212 to Gln-227; Ser-315 to Thr-332; Leu-345 to Phe-354; Asp-362 to Val-370; Thr-518 to Asn-539; Ala-545 to Lys-559; and Val-601 to Pro-610.

SP046

Gln-9 to Ala-18; Glu-179 to Lys-186; Lys-264 to Glu-271; Gly-304 to Glu-17; Ser-503 to Asn-511; Asn-546 to Thr-553; and Asn-584 to Asp-591.

SP048

WO 98/18930 PCT/US97/19422

99

Table 2

S. pneumoniae Antigenic Epitopes

Tyr-4 to Asp-25; Lys-33 to Val-70; Asp-151 to Thr-170; Asp-222 to Val-257; Thr-290 to Phe-301; and Gly-357 to Val-367.

SP049

Ala-23 to Arg-37; Tyr-85 to Gln-95; Glu-106 to Ile-118; Arg-131 to ILE-144; Gly-150 to Ser-162; and Ala-209 to Asp-218.

SP050

Asp-95 to Glu-113; Gly-220 to Gly-228; Asn-284 to Glu-295; Thr-298 to Val-315.

SP051

Lys-16 to Glu-50; Lys-57 to Asn-104; Ser-158 to Trp-173; Asp-265 to Pro-279; Val-368 to Tyr-386; Glu-420 to Ile-454; Pro-476 to Ile-516; Phe-561 to Gly-581; Thr-606 to Gly-664; and Glu-676 to Val-696.

SP052

Asn-41 to Tyr-60; Phe-80 to Glu-103; Ala-117 to Val-139; Ile-142 to Leu-155; Val-190 to Lys-212; Glu-276 to Phe-283; Arg-290 to Ser-299; Leu-328 to Val-351; Gly-358 to Thr-388; Glu-472 to Ala-483; Val-533 to Asn-561; Asp-595 to Val-606; Glu-609 to Val-620; Glu-672 to Ser-691.

SP053

Ala-62 to Val-101; Thr-147 to Leu-174; Lys-204 to Val-216; Gln-228 to Val-262; Ser-277 to Gly-297; Thr-341 to Glyn-368; Thr-385 to Ala-409; Thr-414 to Ser-453; Asn-461 to Leu-490; Glu-576 to Thr-625; Gly-630 to Arg-639; and Asp-720 to Leu-740.

SP054

Glu-7 to Val-28; and Tyr-33 to Glu-44.

Pro-3 to Val-18; Thr-21 to Lys-53; Val-84 to Lys-99; Ile-162 to Val-172; and Val-204 to Ser-241.

SP056

Val-34 to Tyr-41; Leu-47 to Glu-55; and Pro-57 to Gln-66.

Asp-1 to Val-25; Pro-29 to Ile-80; Asn-96 to Val-145; and Pro-150 to Glu-172.

SP058

Ala-64 to Thr-70; Leu-82 to His-138; and Val-228 to Asn-236.

Val-10 to Thr-24; Ser-76 to Pro-102; Ser-109 to Ile-119; Ser-124 to Val-130; Thr-186 to Ile-194; and Asn-234 to Ser-243.

Leu-70 to Arg-76; and Val-79 to Ile-88.

SP062

Glu-14 to Lys-28; Ser-32 to Lys-46; and Glu-66 to Thr-74.

Table 2 S. pneumoniae Antigenic Epitopes

SP063

Ile-10 to Val-25; Val-30 to Thr-40; Asp-44 to Pro-54; Asn-57 to Val-63; Pro-71 to Val-100; and Thr-105 to Thr-116.

SP064

Pro-12 to Leu-32; Val-40 to Leu-68; Asp-95 to Ala-125; Ser-164 to Glu-184; Ser-314 to Glu-346; Asn-382 to Val-393; Leu-463 to Gln-498; Asn-534 to Lys-548; and Lys-557 to Gly-605.

Asn-2 to Ile-12; Ala-39 to Thr-61; and His-135 to Ala-155.

SP067

Gly-1 to Thr-13; Asp-203 to Asn-218; and Gly-240 to Asp-253.

Ser-2 to Ser-12; Val-17 to Gln-26; and Lys-54 to Cys-67.

SP069

Ser-32 to Thr-41; Pro-66 to Glu-80; Thr-110 to Val-122; and Val-147 to Thr-180.

SP070

Lys-6 to Tyr-16; Gln-19 to Ile-27; Arg-50 to Ala-58; Leu-112 to Val-128; Ile-151 to Asn-167; Leu-305 to Phe-321.

SP071

Gln-92 to Asn-158; Gln-171 to Gln-188; Val-204 to Val-240; Thr-247 to Ala-273; Glu-279 to Thr-338; Pro+345 to Glu-368; Asn-483 to Lys-539; Val-552 to Ala-568; Glu-575 to Ser-591; Ser-621 to Gly-640; Gln-742 to Gly-758.

SP072

Val-68 to Tyr-81; Tyr-86 to Val-121; Leu-127 to Gly-140; Gly-144 to Ala-155; Gln-168 to Val-185; Asp-210 to Try-241; Glu-246 to Thr-269; Lys-275 to Tyr-295; Gly-303 to Pro-320; Arg-327 to Ile-335; Thr-338 to Thr-364; Tyr-478 to Phe-495; and Tyr-499 to Arg-521.

SP073

Glu-37 to Val-45; Glu-55 to Val-68; Thr-104 to Thr-119; Ile-127 to Tyr-135; Asn-220 to Ile-232; Thr-237 to Ala-250; Ser-253 to Ala-263; Glu-284 to Ile-297; and Met-438 to Asn-455.

SP074

Gly-2 to Ala-12; Gly-96 to Ile-110; and Thr-220 to Phe-239.

Phe-33 to Tyr-42; Gln-93 to Gly-102; and Val-196 to Asp-211.

SP076

Ser-64 to Leu-76; and Phe-81 to Ala-101.

SP077

Asp-1 to Glu-12; Tyr-26 to Val-35; and Val-51 to Try-62.

Table 2 S. pneumoniae Antigenic Epitopes

SP078

Ala-193 to Ile-208; Tyr-266 to Asn-275; Glu-356 to Leu-369; Ala-411 to Gly-422; Ser-437 to Pro-464; Thr-492 to Glu-534; and Glu-571 to Gln-508.

SP079

Gly-11 to Leu-20; Lys-39 to Leu-48; Leu-72 to Val-85; Asn-147 to Ser-158; Ile-178 to Asp-187; Tyr-189 to Gln-201; and Leu-203 to Ala-216

SPO80

Ser-2 to Glu-12; Gln-42 to Ala-51; Ala-116 to Ser-127; Phe-131 to Asp-143; and Ile-159 to Ile-171.

SP081

Gln-2 to Leu-9; Gln-49 to Cys-57; Ile-108 to Val-131; Gly-134 to Leu-145; and Trp-154 to Cys-162.

SP082

Ile-101 to Ser-187; Gly-191 to Asn-221; Arg-225 to Arg-236; Tyr-239 to Leu-255; and Gly-259 to Arg-268.

SPO83

Ser-28 to Asp-7,0.

SP084

Leu-42 to Gln-66; Thr-69 to Lys-81; Glu-83 to Arg-92; and Gly-98 to Asn-110.

SP085

Gln-2 to Val-22; and Ser-45 to Glu-51.

SP086

Leu-18 to Gln-65; and Lys-72 to Val-83.

SP087

Ser-45 to Leu-53; and Thr-55 to Gln-63

SP088

Pro-8 to Ile-16; Leu-25 to Trp-33; Tyr-35 to Gln-43; Leu-51 to Val-59; Val-59 to Arg-67; Thr-55 to Tyr-63; Asn-85 to Gly-93; Thr-107 to Leu-115;

Leu-115 to Trp-123; Ala-121 to Thr-129; Tyr-153 to Ala-161; His-176 to Gly-184; Tyr-194 to Ala-202; Ala-217 to Gly-225; and Asn-85 to Gly-93.

SP089

Trp-43 to Ala-51; Gln-68 to Phe-76; Val-93 to Gln-101; Phe-106 to Phe-114; Lys-117 to Lys-125; Trp-148 to Phe-156; Glu-168 to Gln-176; Ile-193 to Tyr-201; Lys-203 to Lys-211; Glu-212 to Gln-220; Ile-237 to Tyr-245; Lys-247 to Lys-255; Glu-256 to Gln-264; Met-275 to Gly-283; Lys-286 to Gly-294; Trp-292 to Glu-300; Asp-289 to Thr-297; Tyr-315 to Ser-323; Asp-334 to Lys-342; Pro-371 to Arg-379; Arg-485 to Asn-493; Lys-527 to Arg-535; Phe-537 to Met-545; and Tyr-549 to Glu-557.

SP090

Table 2 S. pneumoniae Antigenic Epitopes

Phe-2 to Gln-10; Gln-13 to Lys-21; Tyr-19 to Glu-27; Tyr-39 to Met-47; Pro-65 to Leu-73; Tyr-121 to His-129; Lys-147 to Ile-155; Gly-161 to Lys-169; Gly-218 to Trp-226; Asp-230 to Thr-238; Tyr-249 to Ala-257; and Ala-272 to Gly-280.

SP091

Ser-19 to Ser-27; Asn-25 to Thr-33; Val-51 to Gln-59; Asn-75 to Asn-83; Ile-103 to Trp-111; Tyr-113 to Ala-121; Leu-175 to Asn-183; Glu-185 to Trp-193; Ala-203 to Tyr-211; Val-250 to Phe-258; Asn-260 to Thr-268; Ser-278 to Asp-286; Tyr-305 to Leu-313; Asn-316 to Gly-324; Asn-374 to Asp-382; Asn-441 to Gly-449; and Ser-454 to Gln-462.

SP092

Arg-95 to Glu-103; Ala-216 to Val-224; Leu-338 to Glu-346; Pro-350 to Ala-358; Pro-359 to Ala-367; Pro-368 to Ala-376; Pro-377 to Ala-385; Pro-386 to Ala-394; Pro-395 to Ala-403; Pro-350 to Ala-358; Gln-414 to Lys-422; Pro-421 to Asn-429; Trp-465 to Tyr-473; Phe-487 to Tyr-495; Asn-517 to Gly-525; Trp-586 to Tyr-594; Phe-608 to Tyr-616; and Asp-630 to Gly-638.

SP093

Gln-30 to Ile-38; Gln-52 to Val-60; Ala-108 to His-116; Tyr-133 to Glu-141; Tyr-192 to Ala-200; and Phe-207 to Ser-215.

SP094

Ala-87 to Val-95; Leu-110 to Cys-118; Gln-133 to Leu-141; Ser-185 to Leu-193; Ile-195 to Gly-203; Asp-206 to Gln-214; Ser-211 to Gly-219; Ile-241 to Thr-249.

SP095

Arg-1 to Gln-9; Phe-7 to Asn-15; Thr-21 to Asn-30; Leu-46 to Phe-54; and Ser-72 to Met-80.

SP096

Gly-29 to Ile-37; Glu-52 to Ser-60; and Leu-64 to Gly-72.

SP097

Ala-11 to Thr-19; Glu-53 to Glu-61; Ser-91 to Lys-99; Thr-123 to Gln-131; and Gly-209 to Lys-217.

SP098

Thr-3 to Ser-11; Gly-38 to Phe-46; Tyr-175 to Asn-183; Met-187 to Cys-195; Gln-197 to Leu-205; Tyr-307 to Gln-315; Gly-318 to Tyr-326; Asn-348 to Val-356; Lys-377 to Pro-385; and Leu-415 to Val-423.

SP099

Arg-19 to Gly-27; Asp-76 to Ser-84; Val-90 to Lys-98; Phe-165 to Val-173; Leu-237 to Pro-245.

SP100

His-111 to Gln-119; Ser-141 to His-149; Asp-154 to Ser-162; Gln-158 to Gln-166; Asp-154 to Gln-166; Lys-180 to Gln-188; and Ser-206 to Gln-214.

SP101

Table 2 S. pneumoniae Antigenic Epitopes

Glu-23 to Glu-31; Glu-40 to Val-48; Gln-50 to Ser-58; Thr-61 to Ile-69; Leu-82 to Ile-90; Ala-108 to Leu-116; Gln-121 to Pro-129; and Leu-130 to Thr-138.

SP102

Asp-32 to His-40; Arg-48 to Lys-56; and Asp-102 to Thr-110.

SP103

Arg-5 to Gln-13; Gln-22 to Leu-30; Arg-151 to Gln-159; Arg-167 to Gln-175; Pro-189 to Glu-197; Gly-207 to Leu-215; Ser-219 to Gln-227; Ser-233 to Ser-241; Pro-255 to Asp-264; Lys-272 to Gly-280; Ser-318 to Val-326; Thr-341 to Asp-351; Asn-356 to Thr-364; Val-370 to Tyr-378; Ile-379 to Gln-387; and Met-435 to Tyr-443.

SP105

Asn-28 to Pro-36; Thr-77 to Phe-85; Arg-88 to Val-96; Gly-107 to Phe-115; Asp-169 to Asp-177; His-248 to Ser-256; and Ser-274 to Ala-282.

SP106

Val-10 to Thr-18; Ile-62 to Tyr-70; Ile-71 to Pro-79; Lys-86 to Gln-94; Lys-100 to Thr-108; Phe-132 to Leu-140; and Asp-145 to Arg-153.

SP107

Asp-33 to Val-41; and Arg-63 to Gln-71.

SP108

Lys-9 to Gln-17; Leu-44 to Ser-52; Ser-63 to Phe+71; Tyr-109 to Ser-117; Ile-183 to Ile-191; Pro-194 to Leu-202; Gly-257 to Gln-265; Ala-323 to Thr-331; and Leu-381 to Tyr-389.

SP109

Asn-2 to Gln-10; Ala-65 to Lys-73; Leu-76 to Glu-84; Thr-111 to Asp-119; Gln-116 to Tyr-124; Tyr-130 to Val-138; Asp-173 to Gly-181; Asp-196 to Ser-204; Asn-231 to Ser-239; Phe-252 to Ser-260; Phe-270 to Tyr-278; Val-291 to His-299; Asp-306 to Leu-314; and Pro-327 to Gly-335.

SP110

Ser-8 to Glu-16; Ile-37 to Val-45; Ala-107 to Val-115; and Gly-122 to Thr-130.

SP111

Asp-19 to Glu-28; Leu-43 to Ala-51; Asn-102 to Phe-110; Gln-133 to Ser-141; Phe-162 to Asp-170; Tyr-194 to Met-202; and Asp-273 to Ser-281.

Table 2 S. pneumoniae Antigenic Epitopes

SP112

Asp-3 to Gln-11; Gly-21 to Ile-29; Ala-46 to Arg-54; Arg-98 to Arg-106; Thr-114 to Val-122; Gln-133 to Asn-141; and Leu-223 to Thr-231.

SP113

Asn-19 to Gly-27; Arg-54 to Ser-62; Val-69 to Gln-77; Ser-117 to Asn-125; Gly-164 to Leu-172; Tyr-193 to Ser-201; Cys-303 to Phe-311; His-315 to Ile-323; Arg-341 to Cys-349; Ile-347 to Ser-355; Arg-403 to Phe-411; Gln-484 to Pro-492; Ser-499 to Leu-507; Ile-541 to Thr-549 Asn-622 to Ile-630; and Glu-645 to Gly-653.

__ . . .

Gly-17 to Leu-25; His-40 to Gln-48; Arg-49 to Arg-57; Ile-65 to Pro-73; Asn-101 to Asp-111; Gly-128 to Cys-136; Phe-183 to Thr-191; and Pro-268 to Ile-276.

SP115

Met-8 to Ser-16; Tyr-24 to Leu-32; Cys-68 to Leu-76; Ser-100 to Pro-108; Thr-193 to Thr-201; Gly-238 to Pro-250; Thr-280 to Phe-288; Pro-303 to Asn-312; Trp-319 to Leu-328; Leu-335 to Leu-344; Lys-395 to Ala-403; Asn-416 to Gln-424; Tyr-430 to Ser-438; Val-448 to Leu-456; Leu-460 to Thr-468; Pro-502 to Thr-510; Lys-515 to Ile-524; Gln-523 to His-532; Tyr-535 to Thr-543; Ser-559 to Pro-567; Thr-572 to Asn-580; Val-594 to Arg-602; Arg-603 to Asn-611; Thr-620 to Trp-628; and Tyr-644 to Arg-653.

SP117

Ala-6 to Gly-14; Ile-19 to Thr-27; Thr-99 to Leu-107; Ser-117 to Asp-125; His-131 to Val-139; Ile-193 to Gly-201; and Val-241 to Gln-249.

SP118

Ser-8 to Trp-23; His-46 to Ala-54; Asn-93 to Gly-101; Val-100 to Ser-108; Arg-155 to Asp-163; and His-192 to Leu-200.

SP119

Tyr-46 to Lys-54; Ser-93 to Ser-101; Trp-108 to Asn-116; Val-121 to Glu-129; and Tyr-131 to Gln-139.

SP120

Ala-57 to Lys-65; Leu-68 to Glu-76; Thr-103 to Tyr-116; Tyr-122 to Val-130; His-163 to Gly-173; Asp-188 to Ser-196; Ser-222 to Ser-231; Phe-244 to Ser-252; Pro-262 to Tyr-270; Val-283 to His-291; and Asp-298 to Leu-306.

SP121

Ser-3 to Ala-11; Asp-13 to Leu-21; Ser-36 to Val-44; and Gln-136 to Met-144.

SP122

Asn-28 to Lys-36; Glu-39 to Thr-50; Val-54 to Lys-62; Asn-106 to Leu-114; Phe-159 to Gly-167; Asn-172 to Arg-180; Glu-199 to Asn-207;

Table 2 S. pneumoniae Antigenic Epitopes

Lys-230 to His-241; Asn-252 to Gly-263; Met-278 to Ala-287; Thr-346 to Asp-354; Lys-362 to Thr-370; Asp-392 to Asn-405; Asp-411 to Ala-424; Gly-434 to Gly-443; Tyr-484 to Glu-492; Ile-511 to Leu-519; Asn-524 to Asp-538; Glu-552 to Ile-567; Val-605 to Lys-613; Phe-697 to Ala-705; Phe-722 to Leu-730; Leu-753 to Leu-761; Asp-787 to Gln-795; Leu-858 to Asn-866; Ala-892 to Thr-901; Gly-903 to Ile-913; Ile-921 to Asn-931; Asn-938 to Pro-951; Gly-960 to Lys-970; Leu-977 to Asp-985; and Leu-988 to Pro-996.

SP123

Val-4 to Asn-12; Glu-47 to Leu-55; Lys-89 to Glu-100; Ser-165 to Thr-173; Lys-234 to Val-242; Ser-258 to Ser-266; Glu-284 to Asn-292; Tyr-327 to Leu-335; Tyr-457 to Thr-465; Tyr-493 to Glu-501; Thr-506 to Tyr-514; Lys-517 to Thr-525; Asn-532 to Gly-540; and Arg-556 to Glu-564.

SP124

rg-16 to Glu-24; Gln-52 to Arg-60; Asn-69 to Tyr-77; Glu-121 to Asn-129; Ala-134 to Val-142; Thr-151 to Ala-159; Asn-164 to Glu-172; His-181 to His-189; Thr-210 to Ala-218; Ser-244 to Val-252; Phe-287 to Tyr-297; Ser-312 to Thr-323; His-433 to Tyr-441; Ser-445 to Asn-453;

Asn-469 to Thr-477; Asn-501 to Asn-509; Gln-536 to Ala-547; and Gln-608 to Asp-621.

SP125

Ser-9 to Asp-21; Ala-28 to Leu-36; Asn-49 to Phe-57; Val-137 to Arg-145; Asn-155 to Leu-163; Glu-183 to Asp-191; Gly-202 to Tyr-210; Pro-221 to Asp-229; Phe-263 to Ala-271; Phe-300 to Gln-308; Asp-313 to Glu-321; Asn-324 to Asp-332; Ile-346 to Asn-354; Asp-362 to Lys-370; Met-402 to Gly-410; Gly-437 to Gly-445; Ser-471 to Glu-483; Gly-529 to Asp-537; Gln-555 to Val-563; and Leu-579 to Lys-587.

SP126

Leu-22 to Thr-30; Val-65 to Leu-73; and Thr-75 to Asp-83.

SP127

Glu-2 to Ala-12; Asp-28 to Thr-36; Val-105 to Thr-113; Lys-121 to Thr-129; Trp-138 to Pro-146; Ser-152 to Ile-160; Lys-180 to Asp-188; Leu-194 to Asn-202; and Gly-228 to Thr-236.

Table 3
S. pneumoniae ORF Cloning Primers

Primer		•	
Name	SEO ID	Sequence	RE
SP001A	NO:227	GACTGGATCCTAAAATCTACGACAATAAAAATC	Bam HI
SP001B	NO:228	CTGAGTCGACTGGTTGTGCTGGTTGAG	Sal I
SPOO4A	NO:229	GTCAGGATCCAAATTACAATACGGACTATG	Bam HI
SP004B	NO:230	CAGTGTCGACTAACTCTAGGTCGGAAAC	Sal I .
SP006A	NO:231	GACTGGATCCTGAGAATCAAGCTACACCCAAAGAG	Bam HI
SPOO6B	NO:232	AGTCAAGCTTTTGTAACTGAGATTGATCTGG	Hind III
SP007A	NO:233	GACTGGATCCTGGTAACCGCTCTTCTCGTAACGCAGC	Bam HI
SP007B	NO:234	AGTCAAGCTTTTTCAGGAACTTTTACGCTTCC	Hind III
SPOORA	NO:235	AGTCAGATCTTGTGGAAATTTGACAGGTAACAGCAAAAAAGCTGC	Bgl II
SP008B	NO:236	ACTGAAGCTTTTTTGTTTTTCAAGAATTCATCG	Hind III
SPO09A	NO:237	GACTGGATCCTGGTCAAGGAACTGCTTCTAAAGAC	Bam HI
SP009B	NO:238	AGTCAAGCTTTCACAAATTCGTTGGTGAAGCC	Hind III
SP010A	NO:239	GACTGGATCCTAGGTCAGGTGGAAACGCTGGTTCATCC	Bam HI
SP010B	NO:240	AGTCAAGCTTATCAACTTTTCCACCTTCAACAACC	Hind III
SP011A	NO:241	GTCAAGATCTCTCCAACTATGGTAAATCTGCGGATGG	Bgl II
SP011B	NO:242	AGTCCTGCAGATCCACATCCGCTTTCATCGGGTTAAAGAAGG	Pst I
SP012A	NO:243	GACTGGATCCTGGGAAAAATTCTAGCGAAACTAGTGG	Bam HI
SP012B	NO:244	GTCACTGCAGCTGTCCTTCTTTTACTTCTTTGGTTGC	Pst I
SP013A	NO:245	GACTGGATCCTGCTAGCGGAAAAAAAGATACAACTTCTGG	Bam HI 🕟
SP013B	NO:246	CTGAAAGCTTTTTTGCCAATCCTTCAGCAATCTTGTC	Hind III
SP014A	NO:247	GACTAGATCTTGGCTCAAAAAATACAGCTTCAAGTCC	Bgl II
SP014B	NO:248/	AGTCCTGCAGGTTTTTGTTTGCTTGGTATTGGTCG	Pst I
SP015A	NO:249	GACTGGATCCTAGTACAAACTCAAGCACTAGTCAGACAGA	Bam HI
SP015B	NO:250	CAGTCTGCAGTTTCAAAGCTTTTTGTATGTCTTC	Pst I
SP016A	NO:251	GACTGGATCCTGGCAATTCTGGCGGAAGTAAAGATGC	Bam HI
SP016B	NO:252	AGTCAAGCTTGTTTCATAGCTTTTTTGATTGTTTCG	<i>Hin</i> d III
SP017A	NO:253	GACTGGATCCTTCACAAGAAAAAACAAAAAATGAAGATGG	Bam HI
SP017B	NO:254	AGTCAAGCTTATCGACGTAGTCTCCGCCTTC	Hind III
SP019A	NO:255	GACTGGATCCGAAAGGTCTGTGGTCAAATAATCTTACC	Bam HI
SP019B	NO:256	AGTCAAGCTTAGAGTTAACATGGTGCTTGCCAATAGG	Hind III
SP020A	NO:257	GACTGGATCCAAACTCAGAAAAGAAAGCAGACAATGC	Bam HI
SP020B -	NO:258	AGTCAAGCTTCCAAACTGGTTGATCCAAACCATCTG	Hind III
SP021A	NO:259	GACTGGATCCTTCGAAAGGGTCAGAAGGTGCAGACC	Bam HI
SP021B	NO:260	AGTCAAGCTTCTGTAGGCTTGGTGTGCCCCAGTTGC	Hind III
SP022A	NO:261	CTGAGGATCCGGGGATGGCAGCTTTTAAAAATC	Bam HI
SP022B	NO:262	CAGTAAGCTTGTTTACCCATTCACCATTACC	Hind III
SP023A	NO:263	CAGTGGATCCAGACGAGCAAAAAATTAAG	Bam HI
SP023B	NO:264	TCAGAAGCTTGTTTACCCATTCACCATT	Hind III
SP025A	NO:265	GACTGGATCCCTGTGGTGAGGAAGAAACTAAAAAG	Bam HI
SP025B	NO:266	CTGAGTCGACAATATTCTGTAGGAATGCTTCGAATTTG	Sal I
SP028A	NO:267	CTGAGGATCCGACTTTTAACAATAAAACTATTGAAGAG	Bam HI
SP028B	NO:268	GTCACTGCAGGTTGTCACCTCCAAAAATCACGG	Pst I
SP030A	NO:269	GACTGGATCCCTTTACAGGTAAACAACTACAAGTCGG	Bam HI
SP030B	NO:270	CAGTAAGCTTTTCGAAGTTTGGCTCAGAATTG	Hind III
SP031A	NO:271	GACTGGATCCCCAGGCTGATACAAGTATCGCA	Bam HI
SP031B	NO:272	CAGTAAGCTTATCTGCAGTATGGCTAGATGG	Hind III
SP032A	NO: 273	GACTGGATCCGTCTGTATCATTTGAAAACAAAGAAAC	Bam HI
SP032B	NO:274	CAGTCTGCAGTTTTACTGTTGCTGTGCTTGTG	Pst I
SP033A	NO:275	ACTGAGATCTTGGTCAAAAGGAAAGTCAGACAGGAAAGG	Bgl II
SP033B	NO:276	CAGTAAGCTTATTCCTGAGCTTTTTTGATAAAGGTTGCGCA	Hind III
SP034A	NO:277	ACTGGGATCCGAAGGATAGATATATTTTAGCATTTGAGAC	Bam HI
SP034B	NO:278	AGTCAAGCTTCCATGGTATCAAAGGCAAGACTTGG	Hind III
SP035A	NO:279	GTCAGGATCCGGTAGTTAAAGTTGGTATTAACGG	Bam HI
SP035B	NO:280	AGTCAAGCTTGCAATTTTTGCGAAGTATTCCAAGAG	Hind III
SP036A	NO:281	AGTCGGATCCTTCTTACGAGTTGGGACTGTATCAAGC	Bam HI

Table 3
S. pneumoniae ORF Cloning Primers

Primer		•	
Name	SEQ ID	Sequence	<u>R E</u>
SP036B	NO:282	AGTCAAGCTTGTTTATTTTTTCCTTACTTACAGATGAAGG	Hind III
SP038A	NO:283	AGTCGGATCCTACTGAGATGCATCATAATCTAGGAGC	Bam HI
SP038B	NO:284	TCAGCTCGAGTTCTTTGACATCTCCATCATAAGTCGC	Xho I
SP039A	NO:285	GACTGGATCCGGTTTTGAGAAAGTATTTGCAGGGG	Bam HI
SP039B	NO:286	CAGTAAGCTTGGATTTTTCATGGATGCAATTTTTTTGG	Hind III
SP040A	NO:287	GACTGGATCCGACAACATTTACTATCCATACAGTAGAGTCAGC	Bam HI
SP040B	NO:288	GACTAAGCTTGGCATAAGGTTGCAATTCTGGATTAATTGG	Hind III
SP041A	NO:289	GACTGGATCCGGCTAAGGAAAGAGTGGATG	Bam HI
SP041B	NO:290	GACTAAGCTTTTCATTTTAAATTGACTATGCGCCCG	Hind III
SP041B	NO:291	GACTGGATCCTTGTTCCTATGAACTTGGTCGTCACC	Bam HI
SP042B	NO:292	CATGAAGCTTATCCTGGATTTTTCCAAGTAAATCT	Hind III
SP042B	NO:293	GACTGGATCCTTATAAGGGTGAATTAGAAAAAGG	Bam HI
SP043A	NO:294	GACTAAGCTTCTTATTAGGATTGTTAGTAGTTG	Hind III
SP043B	NO:295	GACTGGATCCGAATGTTCAGGCTCAAGAAAGTTCAGG	Bam HI
SP044B	NO: 296	GACTAAGCTTTTCCCCTGATGGAGCAAAGTAATACC	Hind III
SP045A	NO:297	GACTGGATCCCTTGGGTGTAACCCATATCCAGCTCCTTCC	Bam HI
SP045A	NO:298	GACTGTCGACTTCAGCTTGTTTATCTGGGGTTGC	Sal I
SP045B	NO:299	GACTGGATCCTAGTGATGGTACTTGGCAAGGAAAACAG	Bam HI
SP046B	NO:300	ACTGCTGCAGATCTTTGCCACCTAGCTTCTCATTG	Pst I
SP048A	NO:300	GTCAGGATCCTGGGATTCAATATGTCAGAGATGATACTAG	Зат НІ
SP048B	NO:302	CTAGAAGCTTACGCACCCATTCACCATTATCATTG	Hind III
SP040B		GTCAGGATCCGGATAATAGAGAAGCATTAAAAACC	Bam HI
SP049B	NO:304	AGTCAAGCTTGACAAAATCTTGAAACTCCTCTGGTC	Hind III
SP050A	NO:304	GTCAGGATCCAGATTTTGTCGAGGAGTGTCATACC	Bam HI
SP050B	NO:306	AGTCAAGCTTTCCCTTTTTACCCTTACGAATCCAGG	Hind III
SP051A	NO:307	GACTGGATCCATCTGTAGTTTATGCGGATGAAACACTTATTAC	Bam HI
SP051B	NO:308	GACTGTCGACGCTTTGGTAGAGATAGAAGTCATG	Sal I
SP052A	NO:309	GACTGGATCCTTACTTTGGTATCGTAGATACAGCCGGC	Bam HI
SP052B	NO:310	AGTCAAGCTTTGTTAATTGCGTACCTTCTAAGCGACC	Hind III
SP053A	NO:311	GACTGGATCCAGCTAAGGTTGCATGGGATGCGATTCG	Sam HI
SP053B	NO:312	GACTGTCGACCTGGGCTTTATTAGTTTGACTAGC	Sal I
SP054A	NO:313	CAGTGGATCCCTATCACTATGTAAATAAAGAGA	Bam HI
SP054B	NO:314	ACTGAAGCTTTTCTGTCCCTGTTTGAGGCA.	Hind III
SP055A	NO:315	CAGTGGATCCTGAGACTCCTCAATCAATAACAAA	Bam HI
SP055B	NO:316	ACGTAAGCTTATAATCAGTAGGAGAAACTGAACT	Hind III
SP056A	NO:317	CAGTGGATCCGGATGCTCAAGAAACTGCGG	Bam HI
SP056B	NO:318	GACTAAGCTTTTGCCTCTCATTCTTGCTTCC	Hind III
SP057A	NO:319	CAGTGGATCCCGACAAAGGTGAGACTGAG	Bam HI
SP057B	NO:320	ACGTAAGCTTATTTCTTAATTCAAGTGTTTTCTCTG	Hind III
SP058A	NO:321	GACTGGATCCAAATCAATTGGTAGCACAAGATCC	Bam HI
SP058B	NO:322	CAGTGTCGACATTAGGAGCCACTGGTCTC	Sal I
SP059A	NO:323	CAGTGGATCCCAAACAGTCAGCTTCAGGAAC	Bam HI
SP059B	NO:324	GACTCTGCAGTTTAATCTTGTCCCAGGTGG	Pst I
SP060A	NO:325	GACTGGATCCATTCGATGATGCGGATGAAAAG	Bam HI
SP060B	NO:326	GACTAAGCTTCATTTGTCTTTGGGTATTTCGCA	<i>Hin</i> d III
SP062A	NO:327	CAGTGGATCCGGAGAGTCGATCAAAAGTAG	Bam HI
SP062B	NO:328	GTCACTGCAGTTGCTCGTCTCGAGGTTC	Pst I
SP063A	NO:329	CAGTGGATCCATGGACAACAGGAAACTGGGAC	Bam HI
SP063B	NO:330	CAGTAAGCTTATTAGCTTCTGTACCTGTGTTTG	Hind III
SP064A	NO:331	GACTGGATCCCGATGGGCTCAATCCAACCCCAGGTCAAGTC	Bam HI
SP064B	NO:332	GACTCTGCAGCATAGCTTTATCCTCTGACATCATCGTATC	Pst I
SP065A	NO:333	GACTGGATCCTTCCAATCAAAAACAGGCAGATGG	Bam HI
SP065B	NO:334	GACTAAGCTTGAGTCCCATAGTCCAAGGCA	Hind III
SP067A	NO:335	AGTCGGATCCTATCACAGGATCGAACGGTAAGACAACC	Bam HI
SP067B	NO:336	ACTGGTCGACTTCTTTTAACTCCGCTACTGTGTC	Sal I
		-	

Table 3
S. pneumoniae ORF Cloning Primers

		S. pheumoniae Orr Cloning Filmers	
Primer			n 50
Name		Sequence	<u>R</u> E
SP068A	NO:337	CAGTGGATCCAAGTTCATCGAAGATGGTTGGGAAGTCC	Bam HI
SP068B	NO:338	GATCGTCGACCCGCTCCCACATGCTCAACCTT	Sal I
SP069A	NO:339	TGACGGATCCATCGCTAGCTAGTGAAATGCAAGAAAG	Bam HI
SP069B	NO:340	TGACAAGCTTATTCGTTTTTGAACTAGTTGCTTTCGT	Hind III
SP070A	NO:341	GACTGGATCCGCACCAGATGGGGCACAAGGTTCAGGG	Bam HI
SP070B	NO:342	TGACAAGCTTAACTTGTAACGAACAGTTCAATCTG	Hind III
SP071A	NO:343	GACTAGATCTTTTTAACCCAACTGTTGGTACTTTCC	Bgl II
SP071B	NO:344	TGACAAGCTTGTTAGGTGTTACATTTTGACCGTC	Hind III
SP072A	NO:345	ACTGAGATCTTTTTAACCCAACTGTTGGTACTTTC	Bgl II
SP072B	NO:346	GACTAAGCTTTCTACGATAACGATCATTTTCTTTACC	Hind III
SP073A	NO:347	GACTGTCGACTCGTAGATATTTAAGTCTAAGTGAAGCG	Sal I
SP073B	NO:348	AGTCAAGCTTGTTAGGTGTTACATTTTGCAAGTC	Hind III
SP074A	NO:349	GACTGGATCCCTTTGGTTTTGAAGGAAGTAAG	Bam HI
SP074B	NO:350	TGACCTGCAGACGATTTTTGAAAAATGGAGGTGTATC	Pst I
SP075A	NO:351	CAGTGGATCCCTACTACCTCTCGAGAGAAAG	Bam HI
SP075B	NO:352	ACTGAAGCTTTTCGCTTTTTACTCGTTTGACA	Hind III
SP076A	NO:353	CAGTGGATCCTAAGGTCAAAAGTCAGACCGCTAAGAAAGTGC	Bam HI
SP076B	NO:354	CAGTAAGCTTTAGGGTATCCAAATACTGGTTGTTGATG	Hind III
SP077A	NO:355	TGACAGATCTTGACGGGTCTCAGGATCAGACTCAGG	Bgl II
SP077B	NO:356	TGACAAGCTTCAAAGACATCCACCTCTTGACCTTTG	Hind III
SP078A	NO:357	GACTGGATCCTAGAGGCTTTGCCAAATGGTGGGAAGGG	Bam HI
SP078B		GTCAGTCGACTTGTTGTAACACTTTTCGAGGTTTGGTACC	Sal I
SP079A	NO:359	CAGTGGATCCTCAAAAAGAGAAGGAAAACTTGG	Bam HI
SP079B	NO:360	CAGTCTGCAGTTTCTTCAACAAACCTTGTTCTTG	Pst I
SP080A	NO:361	CAGTGGATCCACGTTCTATTGAGGACCACTT	Bam HI
SP080B	NO:362	CAGTAAGCTTTTCCTTCTCAGTCAATTCTTTTCC	Hind III
SP081A	NO:363	GACTGGATCCCGCTCAAAATACCAGAGGTGTTCAG	Bam HI
SP081B	NO:364	GACTAAGCTTAGTACCATGGGTGTGACAGGTTTGAA	Hind III
SP082A	NO:365	CTGAGGATCCAATTGTACAATTAGAAAAAGATAGC	Bam HI
SP082B	NO:366	TGACAAGCTTGCGTTGACTAGGTTCTGCAATGCC	Hind III
SP083A	NO:367	GACTGGATCCTCTGACCAAGCAAAAAGAAGCAGTCAATGA	Bam HI
SP083B	NO:368	TCAGCAGCTGATCATTGACTTTACGATTTGCTCC	Bgl II
SP084A	NO:369	GACTGGATCCGTCCGGCTCTGTCCAGTCCACTTTTTCAGCG	Bam HI
SP084B	NO:370	TCAGAAGCTTATTTTTTGTTTCCTTAATGCGTT	Hind III
SP085A	NO:371	GACTGGATCCGGGACAAATTCAAAAAAATAGGCAAGAGG	Bam HI
SP085B	NO:372	GTCAAAGCTTTGGCTCTTTGATTGCCAACAACTG	Hind III
SP086A	NO:373	GACTGGATCCTCGCTACCAGCAACAAAGCGAGCAAAAGG	Bam HI
SP086B	NO:374	GACTAAGCTTACTTTTTCTTTTTCCACACGA	Hind III
SP087A	NO:375	CAGTGGATCCGAACCGACAAGTCGCCCACTATCAAGACT	Sam HI
SP087B	NO:376	CTGAAAGCTTTGAATTCTCTTTCTTTTCAGGCT	Hind III
SP088A	NO:377	TCGAGGATCCGGTTGTCGGCTGGCAATATATCCCGT	Bam HI
SP088B	NO:378	CAGTAAGCTTCCGAACCCATTCGCCATTATAGTTGAC	Hind III
SP089A	NO:379	AGTCGGATCCGGCCAAATCAGAATGGGTAGAAGAC	Bam HI
SP089B	NO:380	TGACCTGCAGCTTCTCATTGATTTTCATCATCAC	Pst I
SP090A	NO:381	GACTGGATCCATTTGCAGATGATTCTGAAGGATGG	Bam HI
SP090B	NO:381	TCAGCTGCAGCTTAACCCATTCACCATTCTAGTTTAAG	Pst I
SP090B	NO:382	GACTGGATCCTGTCGCTGCAAATGAAACTGAAGTAGC	Bam HI
SP091A SP091B	NO:383	GACTAAGCTTATACCAAACGCTGACATCTACGCG	Hind III
SP091B SP092A	NO:384 NO:385	AGTCAGATCTTACGTCTCAGCCTACTTTTGTAAGAGC	Bgl II
SP092A SP092B	NO:385	GACTAAGCTTAACCCATTCACCATTGGCATTGAC	Hind III
		CAGTGGATCCTGGACAGGTGAAAGGTCATGCTACATTTGTG	Bam HI
SP093A	NO:387	GACTAAGCTTCAACCATTGAGACCTTGCAACAC	Hind III
SP093B	NO:388	GTCAGGATCCGATTGCTCCTTTGAAGGATTTGAGAGAAACC	Bam HI
SP094A	NO:389	GACTAAGCTTCGATCAAAGATAAGATATATATAAAGT	Hind III
SP094B	NO:390	GACTAAGCTTCGATCAAAGATAAGATAAATATATATAAAGT GACTGGATCCTAGGTCATATGGGACTTTTTTTTCTACAACAAAATAGC	
SP095A	NO:391	GACTGGATCCTAGGTCATATGGGACTTTTTTTCTACAACAAAATAG	- Dan Di

Table 3 S. pneumoniae ORF Cloning Primers

Primer			
Name	SEO ID	Sequence	<u>re</u>
SP095B	NO:392	TGACAAGCTTATCTATCAGCTCATTTAATCGTTTTTG	Hind III
SP096A	NO:393	CTGAGGATCCCAACGTTGAGAATTATTTGCGAATG	Bam HI
SP096B	NO:394	TGACAAGCTTGAGTCTACAAAAGTAATGTAC	Hind III
SP097A	NO:395	GTCAGGATCCCTACTATCAATCAAGTTCTTCAGCC	Bam HI
SP097B	NO:396	TGACAAGCTTGACTGAGGCTTGGACCAGATTGAAAAG	Hind III
SP098A	NO:397	GACTGGATCCGACAAAACATTAAAACGTCCTGAGG	Bam HI
SP098B	NO:398	GACTAAGCTTAGCACGAACTGTGACGCTGGTTCC	Hind III
SP099A	NO:399	GACTGGATCCTTCTCAGGAGACCTTTAAAAATATC	Bam HI
SP099B	NO:400	GACTAAGCTTGTTGGCCATCTTGTACATACC	Hind III
SP100A	NO:401	GACTGGATCCAGTAAATGCGCAATCAAATTC	Bam HI
SP100B	NO:402	AGTCCTGCAGGTATTTAGCCCAATAATCTATAAAGCT	Pst I
SP101A	NO:403	CAGTGGATCCTTACCGCGTTCATCAAGATGTC	Bam HI
SP101B	NO:404	GACTAAGCTTGCCAGATGTTGAAAAGAGAGTG	Hind III
SP102A	NO:405	GACTGGATCCGTGGATGGGCTTTAACTATCTTCGTATTCG	Bam HI
SP102B	NO:406	AGTCAAGCTTGCTAGTCTTCACTTTCCCTTTCC	Hind III
SP103A	NO:407	GACTGTCGACACTAAACCAGCATCGTTCGCAGGA	Sal I
SP103B		CTGACTGCAGCTTCTTGAAGAAATAATGATTGTGG	Pst I
SP105A	NO:409	CAGTGGATCCTGACTACCTTGAAATCCCACTT	Bam HI
SP105A	NO:410	CAGTAAGCTTTTTTTTAAGGTTGTAGAATGATTTCAATC	Hind III
SP106A	NO:411	CAGTGTCGACTCGTATCTTTTTTTGGAGCAATGTT	Sal I
SP106B	NO:412	GACTAAGCTTAAATGTTCCGATACGGGTGATTG	Hind III
SP107A		CAGTGGATCCGGACTCTCTCAAAGATGTGAAAG	Bam HI
SP107R	NO:414	GACTAAGCTTCTTGAGTTTGTCAAGGATTGCTTT	Hind III
SP108A	NO:415	CAGTGGATCCCAAGAAATCCTATCATCTCTTCCAGAAG	Bam HI
SP108B	NO:416	GACTAAGCTTTTCAGAACTAAAAGCCGCAGCTT	Hind III
SP109A	NO:417	GACTGGATCCACGAAATGCAGGGCAGACAG	Bam HI
SP109B	NO:418	CAGTAAGCTTATCAACATAATCTAGTAAATAAGCGT	Hind III
SP110A	NO:419	CAGTGGATCCTGTATAGTTTTTAGCGCTTGTTCTTC	Bam HI
SP110B	NO:420	GTCAAAGCTTTGATAGAGTGTCATAATCTTCTTTAG	Hind III
SP111A	NO:421	GACTGGATCCGTGTCGAGCATATTCTGAAG	Bam HI
SP111B	NO:422	CAGTAAGCTTACTTTTACCATTTCTTTGTTCTGCATC	Hind III
SP112A	NO:423	GACTGTCGACGTGTTTGGATAGCATTCAGAATCAGACG	Sal I
SP112B	NO:424	CAGTAAGCTTCGGAAGTAAAGACAATTTTTCC	Hind III
SP113A	NO:425	CAGTGGATCCGTGCCTAGATAGTATTATTACTCAAAC	Bam HI
SP113B	NO:426	GACTAAGCTTTTTGCTTATTTCTCTCAATTTTTC	Hind III
SP114A	NO:427	CAGTGGATCCCATTCAGAAGCAGACCTATCAAAATC	Bam HI
SP114B	NO:428	ACTGAAGCTTATGTAATTTTTTAGATTTTTCAATATTTTTCAG	Hind III
SP115A	NO:429	AGTCGGATCCTAAGGCTGATAATCGTGTTCAAATG	Bam HI
SP115B	NO:430	GACTAAGCTTAAAATTAGATAGACGTTGAGT	Hind III
SP117A	NO:431	AGTCGGATCCCTGTGGCAATCAGTCAGCTGCTTCC	Bam HI
SP117B	NO:432	GACTGTCGACTTTAATCTTGTCCCAGGTGGTTAATTTGCC	Sal I
SP118A	NO:433	ACTGGTCGACTTGTCAACAACAACATGCTACTTCTGAG	Sal I
SP118B	NO:434	GACTCTGCAGAAGTTTAACCCACTTATCATTATCC	Pst I
SP119A	NO:435	ACTGGGATCCTTGTTCAGGCAAGTCCGTGACTAGTGAAC	Bam HI
SP119B	NO:436	GACTAAGCTTGGCTAATTCCTTCAAAGTTTGCA	Hind III
SP120A	NO:437	AGTCGGATCCCTCGCAAATTGAAAAGGCGGCAGTTAGCC	Bam HI
SP120B	NO:438	GACTAAGCTTGTAAATAAGCGTACCTTTTTCTTCC	Hind III
SP121A	NO:439	TCAGGGATCCTTGTCAGTCAGGTTCTAATGGTTCTCAG	Bam HI
SP121B	NO:440	AGTCAAGCTTGGCATTGGCGTCGCCGTCCTTC	Hind III
SP122A	NO:441	GACTGGATCCGGAAACTTCACAGGATTTTAAAGAGAAG	Bam HI
SP122B	NO:442	GACTGTCGACAATCAATCCTTCTTCTGCACTTCT	Sal I
SP123A	NO:443	CAGTGGATCCTGTGGTCGAAGTTGAGACTCCTCAATC	Bam HI
SP123B	NO:444	GACTAAGCTTTTCTTCAAATTTATTATCAGC	Hind III
SP124A	NO:445	AGTCGGATCCAACACCTGTATATAAAGTTACAGCAATCG	Bam HI
SP124B	NO:446	GACTGTCGACTACTTGACCGAATGCGTCGAATGTACG	Sal I

Table 3 . pneumoniae ORF Cloning Primers

Primer			
Name	SEO ID	Sequence	<u>R.E</u>
SP125A	NO:447	CTGAGGATCCATTAGACAGATTAATTGAAATCGG	Bam HI
SP125B	NO:448	GACTGTCGACTTTAAAGATTGAAGTTTTAAAGCT	Sal I
SP126A	NO:449	TGACGGATCCTAAGACAGATGAACGGAGCAAGGTG	Bam HI
SP126B	NO:450	CTGAAAGCTTTAAGGCTTCCTCAATGAGTTTGTCT	Hind III
SP127A	NO:451	GACTGGATCCCTGTGAGAATCAAGCTACACCCA	Bam, HI
SP127B	NO:452	CTGAAAGCTTTTGTAACTGAGATTGATCTGGGAG	Hind III

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page 9					
B. IDENTIFICATION OF DEPOSIT	Further deposits are identified on an additional sneet				
Name of depositary institution American Type Culture Collection					
Address of depositary institution fincluding postal code and country 12301 Parklawn Drive Rockville, Maryland 20852 United States of America	· ·				
Date of deposit October 10, 1996	Accession Number 55840				
C. ADDITIONAL INDICATIONS (leave blank if not applicable	This information is continued on an additional sheet				
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).					
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)					
E. SEPARATE FURNISHING OF INDICATIONS (leave blank	cif not applicable)				
The indications listed below will be submitted to the International Bin Number of Deposit")	areau later (specify ine general nature of the indications e.g., "Accession				
For receiving Office use only This sheet was received with the international application Authorized officer 12 DECEMBER 1997	For International Bureau use only This sheet was received by the International Bureau on: Authorized officer				

Form PCT/RO/134 (July 1992)

SINGAPORE

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for international publication of the application.

NORWAY

The applicant hereby requests that, until the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegians Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Registration), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ICELAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the Icelandic Patent Office), or has been finally decided upon by the Icelandic Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected in the art.

PCT/US97/19422

113

Page 2

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person approved by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PUT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant, any request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by the applicant in the individual case.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the International publication of the application.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapse, the microorganism shall be made available as provided in Rule 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever two dates occurs earlier.

PCT/US97/19422

5

10

15

20

25

30

35

What Is Claimed Is:

- 1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- (a) a nucleotide sequence encoding any of the amino acid sequences of the polypeptides shown in Table 1; or
- (b) a nucleotide sequence complementary to any of the nucleotide sequences in (a).
- 2. An isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent hybridization conditions to a polynucleotide having a nucleotide sequence identical to a nucleotide sequence in (a) or (b) of claim I wherein said polynucleotide which hybridizes does not hybridize under stringent hybridization conditions to a polynucleotide having a nucleotide sequence consisting of only A residues or of only T residues.
- 3. An isolated nucleic acid molecule comprising a polynucleotide which encodes the amino acid sequence of an epitope-bearing portion of a polypeptide having an amino acid sequence in (a) of claim 1.
- 4. The isolated nucleic acid molecule of claim 3, wherein said epitope-bearing portion of a polypeptide has an amino acid sequence listed in Table 2.
- 5. A method for making a recombinant vector comprising inserting an isolated nucleic acid molecule of claim 1 into a vector.
 - 6. A recombinant vector produced by the method of claim 5.
- 7. A method of making a recombinant host cell comprising introducing the recombinant vector of claim 6 into a host cell.
 - 8. A recombinant host cell produced by the method of claim 7.
- 9. A method of producing a polypeptide encoded by the nucleic acid molecule of claim 1 comprising culturing the host cell of claim 8 under conditions favoring expressing the heterologous polypeptide.

WO 98/18930 PCT/US97/19422

- 10. A polypeptide produced according to the method of claim 9.
- 11. An isolated polypeptide comprising an amino acid sequence at least 70% identical to a sequence selected from the group consisting of an amino acid sequence of any of the polypeptides described in Table 1.
- 12. An isolated polypeptide antigen comprising an amino acid sequence of an *S. pneumoniae* epitope shown in Table 2.
- 13. An isolated nucleic acid molecule comprising a polynucleotide with a nucleotide sequence encoding a polypeptide of claim 9.
- 14. An isolated antibody that binds specifically to a polypeptide of claim 11.
 - 15. A hybridoma which produces an antibody according to claim 14.
 - 16. A vaccine, comprising:

5

10

15

20

25

30

35

- (1) one of more *S. pnuemoniae* polypeptides selected from the group consisting of a polypeptide comprising an amino acid sequence identified in Table 1, or a fragment thereof; and
- (2) a pharmaceutically acceptable diluent, carrier, or excipient; wherein said polypeptide is present, in an amount effective to elicit protective antibodies in an animal to a member of the *Streptococcus* genus.
- 17. A method of preventing or attenuating an infection caused by a member of the *Streptococcus* genus in an animal, comprising administering to said animal a polypeptide of claim 11, wherein said polypeptide is administered in an amount effective to prevent or attenuate said infection.
- 18. A method of detecting *Streptococcus* nucleic acids in a biological sample obtained from an animal involving assaying for one or more nucleic acid sequences encoding *Streptococcus* polypeptides in a sample comprising:
- (a) contacting the sample with one or more of the above-described nucleic acid probes, under conditions such that hybridization occurs, and
- (b) detecting hybridization of said one or more probes to the one or more *Streptococcus* nucleic acid sequences present in the biological sample.

5

10

15

- 19. A method of detecting *Streptococcus* nucleic acids in a biological sample obtained from an animal, comprising:
- (a) amplifying one or more Streptococcus nucleic acid sequences in said sample using polymerase chain reaction, and
 - (b) detecting said amplified Streptococcus nucleic acid.
- 20. A kit for detecting *Streptococcus* antibodies in a biological sample obtained from an animal, comprising
 - (a) a polypeptide of claim 12 attached to a solid support; and
 - (b) detecting means.
- 21. A method of detecting *Streptococcus* antibodies in a biological sample obtained from an animal, comprising
 - (a) contacting the sample with a polypeptide of claim 12; and
 - (b) detecting antibody-antigen complexes.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C12N 15/31, 5/18, 1/21, C07K 14/315, C12Q 1/68, A61K 39/09, G01N 33/569, 33/68

(11) International Publication Number:

WO 98/18930

(43) International Publication Date:

7 May 1998 (07.05.98)

(21) International Application Number:

PCT/US97/19422

(22) International Filing Date:

30 October 1997 (30.10.97)

(30) Priority Data:

60/029,960

31 October 1996 (31.10.96) US

(71) Applicant (for all designated States except US): HUMAN GENOME SCIENCES, INC. [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).

(72) Inventors; and

- (75) Inventors/Applicants (for US only): KUNSCH, Charles, A. [US/US]; 2398B Dunwoody Crossing, Atlanta, GA 30338 (US). CHOI, Gil, H. [KR/US]; 11429 Potomac Oaks Drive, Rockville, MD 20850 (US). JOHNSON, L., Sydnor [US/US]; 13545 Ambassador Drive, Germantown, MD 20874 (US). HROMOCKYJ, Alex [US/US]; 10003 Sidney Road, Silver Spring, MD 20901 (US).
- (74) Agents: BROOKES, A., Anders et al.; Human Genome Sciences, Inc., 9410 Key West Avenue, Rockville, MD 20850 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 8 October 1998 (08.10.98)

(54) Title: STREPTOCOCCUS PNEUMONIAE ANTIGENS AND VACCINES

(57) Abstract

The present invention relates to novel vaccines for the prevention or attenuation of infection by *Streptococcus pneumoniae*. The invention further relates to isolated nucleic acid molecules encoding antigenic polypeptides of *Streptococcus pneumoniae*. Antigenic polypeptides are also provided, as are vectors, host cells and recombinant methods for producing the same. The invention additionally relates to diagnostic methods for detecting *Streptococcus* nucleic acids, polypeptides and antibodies in a biological sample.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	ТJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	. ML	Mali	TT	Trinidad and Tobago
ВJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	, Cameroon .		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		•
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		
							•

Intern:

al Application No PCT/US 97/19422 A. CLASSIFICATION OF SUBJECT MATTER
1PC 6 C12N15/31 C12N5/18 C12N1/21 C07K14/315 C12Q1/68 A61K39/09 G01N33/569 G01N33/68 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) C12N C07K C12Q A61K G01N Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. X WO 95 06732 A (UNIV ROCKEFELLER ; MASURE H 1-21 ROBERT (US); PEARCE BARBARA J (US); TUO) 9 March 1995 SEQ ID nos. 3 and 4 see claims 1-52 C. MARTIN ET AL.: "Relateness of X 1-15 penicillin-binding protein la genes from different clones of penicillin-resistant Streptococcus pneumoniae isolated in South Africa and Spain" EMBO J., vol. 11, no. 11, November 1992, OXFORD UNIVERSITY PRESS,GB; pages 3831-3836, XP002060148 see the whole document -/--Further documents are listed in the continuation of box C. X X Patent family members are listed in annex. Special categories of cited documents : T later document published after the international filing date or priority date and not in conflict with the application but *A* document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the invention *E* earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the *O* document referring to an oral disclosure, use, exhibition or document is combined with one or more other such doc other means ments, such combination being obvious to a person skilled *P* document published prior to the international filing date but later than the priority date claimed in the art. *&* document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 1 8. O**8**. 1998 6 May 1998

Authorized officer

HORNIG H.

Name and mailing address of the ISA

NL - 2280 HV Rijawijk

Fax: (+31-70) 340-3016

European Patent Office, P.B. 5818 Patentiaan 2

Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,

Intern: al Application No
PCT/US 97/19422

(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT				
(WO 96 16082 A (ASTRA AB ;BALGANESH TANJORE SOUNDARARAJA (IN); TOWN CHRISTINE MARY) 30 May 1996 SEQ ID nos. 5 and 6 see claims 1-26	1-15		
1	WO 95 31548 A (UAB RESEARCH FOUNDATION ;YOTHER JANET (US); DILLARD JOSEPH P (US)) 23 November 1995 see the whole document	1-21		
A	WO 95 14712 A (RES CORP TECHNOLOGIES INC) 1 June 1995 see the whole document	1-21		
A	WO 96 05859 A (AMERICAN CYANAMID CO) 29 February 1996 see abstract	1-21		
A	WO 93 10238 A (US HEALTH) 27 May 1993 see the whole document	1-21		
A	EP 0 687 688 A (UNIV OVIEDO ;UNIV LEICESTER (GB)) 20 December 1995 see abstract	1-21		
A	EP 0 622 081 A (UAB RESEARCH FOUNDATION) 2 November 1994 see the whole document	1-21		
A	B.J. PEARCE ET AL.: "Genetic identification of exported proteins in Streptococcus pneumoniae" MOLECULAR MICROBIOL., vol. 9, no. 5, 1993, BLACKWELL, OXFORD, GB, pages 1037-1050, XP002060149 see the whole document	1-21		
	·			
•				

Int tional application No.

PCT/US 97/19422

Box i	Observations where certain claims were found unsear hable (Continuation filtem 1 of first sheet)
This Inte	rmational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Remark: Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
з. 🗌	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	mational Searching Authority found multiple inventions in this international application, as follows:
see	e continuation-sheet
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X	No requiréd additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
•	1-21 partially (subject 1. on continuation-sheet)
Remark o	The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

1. Claims: (1-21) partially

An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence from the group consisting of of: (a) a nucleotide sequence SEQ ID no.1 encoding the the amino acid sequence of the polypeptide SEQ ID no.2 shown in Table 1; or (b) a nucleotide sequence complementary to said nucleotide sequence in (a); an isolated nucleic acid molecule comprising a polynucleotide which hybridizes under stringent conditions to a polynucleotide having a nucleotide sequence identical to a nucleotide sequence in (a) or (b), wherein said polynucleotide which hybridizes does not hybridize under stringent hybridization conditions to a polynucleotide having a nucleotide sequence consisting of only A or of only T residues; an isolated nucleic acid molecule comprising a polynucleotide which encodes the amino acid sequence or an epitope-bearing portion of a polypeptide having an amino acid sequence of SEQ ID no.2 in (a); said epitope-bearing portion of a said polypeptide has an amino acid sequence listed in Table 2; a method of making a vector using said isolated nucleic acid molecule; said recombinant vector; a method of making a recombinant host cell using said vector; said recombinant host cell; a method of producing said polypeptide; said polypeptide; an isolated antibody that binds to said polypeptide; a hybridoma which produces said antibody; a vaccine comprising said polypeptide selected from SEQ ID no.2 in Table 1, or a fragment therof; a method of preventing or attenuating an infection caused by a member of Streptococcus genus in animal using said polypepitde; a method for detecting Streptococcus nucleic acid sequences using the above-described nucleic acid probe; a kit for detecting Streptococcus antibodies in a biological sample using said polypeptide sequence:

2-113. Claims: (1-21) partially

-Idem as subject 1 but limited to the sequences having SEQ ID nos. 3 to 226. (Invention 2 is limited to SEQ ID nos. 3 and 4; Invention 3 is limited to SEQ ID nos. 5 and 6; Invention 113 is limited to SEQ ID nos. 225 and 226).

For the sake of conciseness, the first group is explicitly defined, the other groups are defined by analogy hereto.

mirórmation on patent family members

Intern lai Application No
PCT/US 97/19422

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9506732 A	09-03-95	AU 7680994 CA 2170726 EP 0721506 FI 960977	A 09-03-95
		JP 9504686 NO 960839	T 13-05-97
WO 9616082 A	30 - 05-96	AU 2045895 AU 3088795 CA 2150532 CN 1173182 EP 0792284 FI 972215 GB 2290792 HU 77487 IE 950412	A 11-02-98 A 03-09-97 A 26-05-97 A 10-01-96 A 28-05-98 A 10-01-96 A 01-07-97
WO 9531548 A	23-11-95	AU 2638595 EP 0804582	
WO 9514712 A	01-06-95	US 5474905	A 12-12-95
WO 9605859 A	29-02-96	CA 2198251 EP 0778781	A 14-03-96 A 29-02-96
WO 9310238 A	27-05-93	AU 3065892	A 15-06-93
EP 0687688 A	20 - 12-95	ES 2075803 ES 2088820 WO 9516711	A 16-09-96
EP 0622081 A	02-11-94	AU 682018 AU 5769694 CA 2116261	A 27-10-94

harmation on patent family members

interns al Application No PCT/US 97/19422

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0622081 A		FI 941695 A JP 7126291 A NO 941420 A US 5679768 A ZA 9401584 A	21-10-94 16-05-95 21-10-94 21-10-97 12-10-94

Form PCT/ISA/210 (patent family annex) (July 1992)

n=4- 0 4- 0